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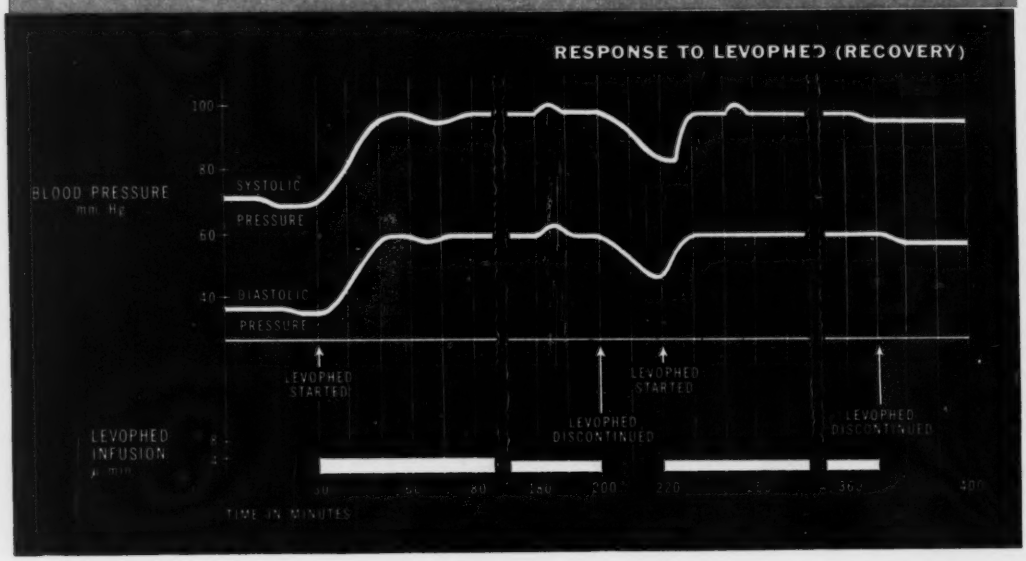
Myocardial Infarction with Severe Shock:



Reduction of Mortality

"... in correcting the state of shock we have enabled certain patients to recover from the initial episode, which otherwise gave every indication of culminating in death."[1]

Levophed infusion causes a striking rise in oxygen tension in areas of myocardial ischemia produced by coronary obstruction.[2] "It is therefore reasonable to suppose that the restoration of arterial pressure to a level consistent with an adequate coronary flow must limit the size of the infarct, save healthy myocardium, shorten the period of shock, and lessen the likelihood of congestive failure at a later date."[3]

"Severe cardiogenic shock demands therapy... the most efficacious method of treatment now available is use of vasopressor drugs."[4] "Current usage favors nor-epinephrine."[5]

References:

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Circulation
A Journal of the American Heart Association
JULY 1954
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The Lewis A. Connor Memorial Lecture

Atherosclerosis. An Introduction

By IRVINE H. PAGE, M.D.

I PROPOSE to cast this lecture in a form I think Dr. Connor would have approved. I say this with some assurance because, when I was a student, he was my professor of medicine at Cornell University Medical School, and coincidentally, a fellow Hoosier. He was aware of, and impressed upon us, the need for understanding the basic science which lies behind most of clinical practice. He was not what we today consider a professional scientist, but his sympathies were with the group of young investigators who were then struggling to close the unsympathetic gap between science and the bedside.

Out of the vast welter of papers concerned with atherosclerosis, I will try to develop trends both investigational and clinical, although I am fully aware of the dangers involved, chief among these being that my knowledge and judgment are inadequate to the task. Thus you will not find the exhaustive documentation required of more rigorous presentations. Instead you will find many opinions which reflect often only my views, ephemeral I trust and hope as an earnest of progress.

As a point of departure, I list those things on which we can probably all agree.

1. Atheromatosis is civilized man's greatest killer.
2. Knowledge of its nature is primitive.
3. No method of antemortem diagnosis is available.
4. Its occurrence is focal.
5. It can be reproduced with uncertain fidelity in many animals, usually under highly abnormal conditions.
6. Hyperlipemia and hypertension, aging, heredity, maleness and arterial anatomy predispose.
7. Lipids are the only large class of vital substances insoluble in water.
8. Proteins may be as important as lipids in its genesis.
9. Countries on high caloric, high lipid diets have a high incidence.

A few words about the present social status of the subject: it is just about to take on respectability. Confident statements and remarkable observations of this type, "as the degree of coronary atherosclerosis increased, so did the incidence of psychic trauma," will, we can hope, be at an end. It is essential that the critical atmosphere of science replace the residual superstitions of the medicine man; that evidence be criticized without fear or favor as it accumulates; that the absurdities of quackish exploitation be labeled as such; and, finally, that the cardiologist assume the burden of atherosclerosis which he has so long and so successfully avoided in favor of taking care of its consequences.

We must expect atherosclerosis to be "cured" and its "cause" proclaimed at least twice a year for the next 10 years or so. It is part of the natural history of discovery that emotions outpace logic. This is a sign of health. It must be remembered that this is a very new field with a relatively poor backlog of knowledge. Almost

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anything that turns up is new; even most of the investigators are new and quite shiny.

Recall that the structure of cholesterol was elucidated only 26 years ago by men such as Rosenheim—of whom most young "steroid" chemists have never heard—and that at that time it had essentially no metabolism: it was an inert structural material without obvious function. We were thrilled when it was shown later to be synthesized and degraded in the animal body, even though isotopic and other more rigorous technics were not available to give final proof. Those early battles with neglect and prejudice have at least been won, and the young investigator now has the tools of his trade and the political setting of societies and initial respectability.

I won't bother you with a discussion of the problem of nomenclature except to say that *athero* derives from the Greek word meaning "mush." Dr. Perry Pepper has pointed out that electronic science derives from the Greek name, "Elektron," for amber, because of the electrostatic phenomena observed when amber is rubbed. We can only hope that our etymologic future will not be forever mush, as theirs is forever amber.

I shall use the word lipid to include all fatty materials such as neutral fat, cholesterol, phospholipid, etc. Phosphatide I prefer to phospholipid but usage seems to be against me.

I have not heavily documented the evidence with literature references. This will doubtless cause many of my friends some anguish. I can only plead that I seldom adopt this form, even out of consideration for the reader. For those who want references, I have appended a list of readily available reviews; the bibliography of Katz and Stamler's, "Experimental Atherosclerosis," is especially good.

A word about the antiquity of the problem. Ruffer finds that the old Egyptians suffered from arterial lesions identical with those prevalent today, possibly in like incidence, and with almost as little insight into its etiology. At least it was not attributed to tobacco since Egyptians didn't smoke. Nor were they inclined to be drunkards. Meat was a luxury and the diet was mostly vegetable, and often very coarse, as is shown by the worn crowns of the teeth. Presumably the wear, tear and stress of building pyramids, the Ethiopian expeditions, the Red Sea disaster and the precedent plagues, and paying for them by taxes, imposed burdens comparable to those we suffer today. No reason is known why arterial disease with the modern anatomic characteristics should have been so common in ancient Egypt. An interlude of some 3000 years seems unreasonably long to wait before man has undertaken to do something about a disease so prevalent and lethal.

While most of the testimony marshalled in this lecture is concerned with lipids, I believe it should be strongly emphasized that this reflects the current preoccupation with this class of compounds. There is clear evidence that subendothelial fibroblastic proliferation, defects in the inner elastic lamella and changes in the ground substance often are quite as impressive and may even precede the lipid changes of atherosclerosis. While in some experimental animals lipid infiltration alone seems to be adequate for atherogenesis, in man predisposing factors seem more important; lipid infiltration may be primary or secondary, depending on the particular circumstances.

The time seems right for a change in the tactics of research to include mechanisms other than those directly concerned with lipids, though it will be recognized that many of these will be concerned with problems of the synthesis of lipoproteins and the removal of lipids from them. But those mechanisms having less to do with lipids such as changes in ground substance, subendothelial proliferative changes and their causes should not suffer from inattention.

Filtration Concept of Atherosclerosis

The investigation of atherosclerosis has been plagued for 50 years or more with theories, most of them based purely on impression. They explained little because they rested on so little solid fact. Today, with experiments making such rapid progress, you may forgive me in proposing in outline a concept which I find helpful as a working hypothesis and as a skeleton on which to hang facts in some sort of order.

This "filtration" concept is based on the view that atherogenesis is due to the tissue reaction to substances filtered from plasma as lipoprotein by lateral arterial pressure, and deposited in the intima as "foreign" lipid. Most of the filtered materials pass on harmlessly to be picked up by the adventitial capillaries or the lymph. But some may stay behind, whether because the vessel fails to function properly as a filter or because the size, shape and charge of the lipoproteins is such as to allow them to stick. Changes in the arrangement, amount and chemical nature of subendothelial ground substance conceivably may initiate a focal change in filter function. The reaction which ensues depends on the nature of the lipid deposited and the responsiveness of the tissues to it. In this view, factors in atherogenesis are:

1. The anatomy, biochemistry and physiology of the vessel wall, all of which are hereditarily conditioned.
2. The composition of plasma.
3. The lateral arterial pressure and rate of filtration.
4. The responsiveness of intimal tissues to filtered products and their degradation products, normal or abnormal.
5. The metabolic capacity of the vessel wall.
6. Changes in filtration capacity of the vessel wall, such as may result from age, hypertensive diseases and metabolic disorders.

The words in this outline have been chosen with care to be precise but inclusive. I will not discuss the constituents of this hypothesis because they seem self evident, and each will receive at least some comment in the discrete sections of this address.

Early in the course of the disease the vessels show a slowly progressive increase in total lipid content, the composition of which is much like that of plasma. In general, this pattern is maintained until the chemically more stable substances begin to accumulate more rapidly in areas without adequate nutrition. Briefly, the pertinent evidence is as follows:

1. Total lipids, free and ester cholesterol, phospholipid, both lecithin and sphingomyelin, and neutral fat increase, especially early in the disease.

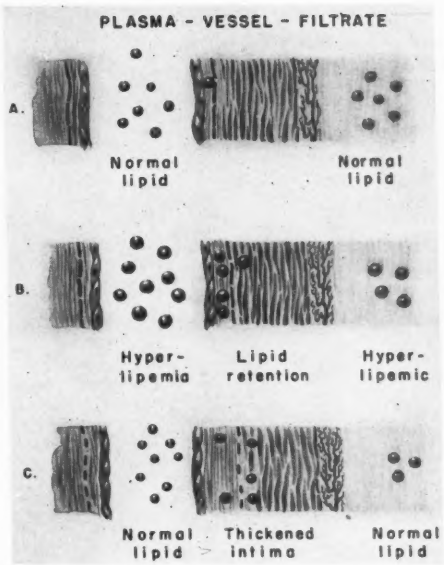

FIG. 1. Schematic representation of filtration theory of atherogenesis. (A) Normal plasma lipids with normal arterial wall. The passage of lipoproteins through the internal elastic membrane is depicted and their appearance in the lymph and adventitial blood. (B) Hyperlipemic plasma with greater lipid retention in normal arterial wall. (C) Normal plasma lipids passing through an arterial wall with thickened intima and fragmented internal elastic lamina.

2. As necrosis occurs, neutral fat, phospholipid and free cholesterol tend to decrease.
3. As the lesion advances, ester cholesterol, the small amounts of dihydrocholesterol and cholestenone increase disproportionately.

Perhaps the important point which needs emphasis is the basic similarity in initial relative composition of vessel wall and plasma lipid. This supports the view that the source of the vessel wall lipid is plasma lipid. The beta lipoprotein is probably the chief carrier in plasma of unstably held lipid which would be shed within the vessel as the filtered lipoprotein breaks down. This lipid is then "foreign" and the nidus of a foreign body reaction.

This concept involves much more than lipid. Atherosclerosis results from the collaboration of a variety of mechanisms; defining one without reference to the other parameters

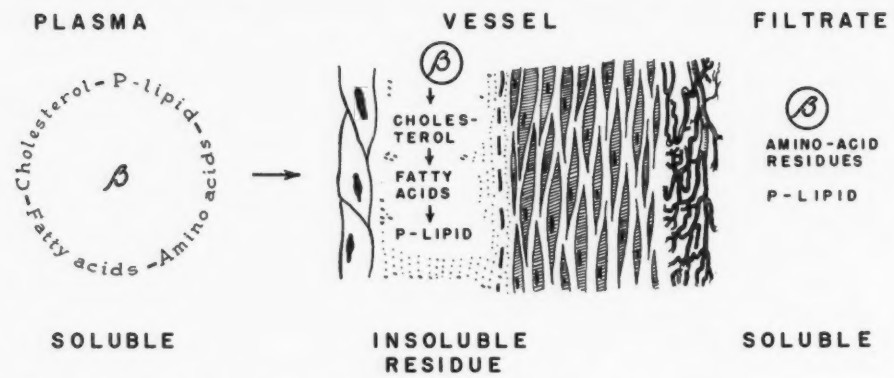

FIG. 2. Schematic representation of passage of lipoproteins through an arterial wall with disruption of the heavily lipid-laden lipoprotein within the wall to give an insoluble residue which provokes tissue reaction.

of the problem can only lead to what President Roosevelt used to call a very "iffy" answer.

This concept depends on the demonstration that there is in fact large movement of plasma constituents through vessel walls. The testimony supporting this view is:

1. Perfusion of isolated dead blood vessels demonstrates the filtration and the passage of macromolecules through the vascular filter bed.

2. The lipid composition, even to fatty acid pattern of the cholesterol esters of human aorta, is similar to that in serum.

3. The capillaries of blood vessels provide a means of exchange between the blood stream and lymph. This may account for the facts that lymph has much the same qualitative lipoprotein pattern as plasma and the appearance of abnormal proteins in plasma is usually associated with their appearance in lymph.

4. There is no parallelism between cholesterol concentrations in serum and aorta with advancing age, but with the high lateral pressures of essential hypertension aortic cholesterol increases at a rapid rate while serum cholesterol remains normal.

5. Injected marcromolecules other than lipids accumulate beneath the intima. Polyvinyl alcohol is an example.

6. Exogenous cholesterol seems to form the bulk of the cholesterol in the atheroma of cholesterol-fed rabbits.

Lastly, the tissue responses need emphasis. Changes in the subintimal ground substance and fibroblastic proliferation are believed by some to precede lipid deposition. The degree of fibroblastic response may to some extent determine the amount of vascular damage.

EXPERIMENTAL ATHEROGENESIS

Our interest here will be confined to searching for some general principles which might bear on the mechanism of human disease. The literature on the experimental aspect is large and one cannot always evaluate the results with assurance. I list below the factors prediposing to experimental atherogenesis.

Factors Predisposing to Experimental Atherogenesis

1. Injury to the vessel by cold, allylamine, intimal hemorrhage, trauma.

2. Changes in the nature of the acid mucopolysaccharide ground substance by hyaluronidase or other means, such as scorbutic diets in guinea pigs. Loss of continuity of internal elastic membrane especially in cerebral vessels.

3. Hypertension.

4. High fat and caloric intake with weight increase.

5. "Dietary factor" (Holman) contained in cod liver oil, etc.

6. Choline-deficiency in rats.

7. Factors altering absorption of lipid such as cholic acid and detergents (Tween-80).

8. Age and sex in cholesterol feeding experiments.

9. Reduction of thyroid activity.

10. Elevation of blood lipids by stilbestrol, some adrenal steroids, Aureomycin, ureter ligation.

11. Inability of the liver in some animals, such as rabbits, effectively to prevent hyperlipemia.

12. Calcification of senescent elastic medial tissue and medial degeneration.

Their wide variety is immediately evident. Doubtless there are many more. Some believe these predisposing factors a necessary prelude to the deposition of lipid; others do not. The too hasty attribution of atherogenesis to any one factor, no matter how appealing, can only lead to a distorted concept of the disease.

Experimental atherosclerosis is usually induced by feeding cholesterol dissolved in oil. But the following list shows many other ways.

Methods of Experimental Atherogenesis

1. Cholesterol feeding in rabbits, guinea pigs, hamsters, pigs, chickens.

2. Cholesterol and thiouracil feeding in normal dogs or dogs with renal hypertension.

3. Cholesterol feeding with diets low in sulfur amino acids in monkeys.

4. Hyperlipemia induced by stilbestrol or by thyroidectomy plus hypophysectomy.

5. Intravenous injection of lipoproteins or of egg yolk and emulsions of cholesterol, 7-keto- or 7-hydroxycholesterol with or without prior injury of the wall with substances such as allylamine or by freezing.

6. Pyridoxin-deficient diets in monkeys.

7. Choline-deficiency in rats?

8. Renal hypertension, cholesterol and methyl thiouracil feeding in rats?

The effectiveness of the cholesterol diet may be greatly increased by depressing thyroid function with thiouracil or radioiodine and further augmented by establishment of renal hypertension. Feeding diets low in the sulfur-containing amino acids, and possibly pyridoxine deficiency, also increases its effectiveness. An interesting new method depends on the intravenous injection into normal rabbits of plasma from cholesterol-fed rabbits. Another depends on injection of lipoprotein concentrates into rats. As you know, it has not been possible to produce atheroma in rats by feeding diets which would be highly atherogenic in other species; even though the blood lipids are greatly elevated, no atheroma appears. However, rats given 30 successive daily injections of concentrates of lipoproteins from cholesterol-fed rabbits by Bragdon manifest early lesions in the endocardium. So far, this procedure has not elicited striking coronary or aortic lesions. Quite recently Malinow believes he has produced generalized atherosclerosis in rats made hypertensive by Page's method, and fed cholesterol and methyl thiouracil. Choline deficiency in rats causes deposition of lipid in the endothelial cells, and later proliferation of the intimal cells occurs with formation of small plaques. In the carotid arteries and aorta the subjacent media undergo necrosis and ultimate calcification, according to Hartroft. Obese male rats given nephrotoxic antiserum followed by daily injection of desoxycorticosterone acetate (DCA) and saline to drink were said by Wisler to become atherosclerotic. All this work requires much elaboration before it can be accepted as established.

Most methods depend on raising the plasma level of lipids to very high values usually by feeding cholesterol in oil for several months, or, in the case of the less susceptible animals, for a year or more. The only exception appears to be the atheroma produced by intravenous injection, when the hyperlipemia is short lived. Whether this is due to some special lipoprotein which was injected remains to be demonstrated. The feeding of neutral fat alone does not appear to be a sufficient stimulus.

I have included the work of Evans and of Wilens on the production of lipid infiltration of vessels because it shows the great importance of mechanical factors in atherogenesis. Using dead vessels and a pump for transarterial perfusion, they showed that a large amount of filtrate is formed and that much lipid was caught in the vessel wall. This is not to say that such experiments reproduce atherogenesis in viable vessels. Thus artificial deposits are frequently found in the outer zone of the media, a site almost never involved in spontaneous lipidosis. In life, probably, lipids which penetrate beyond the intima would meet no further

TABLE 1.—*Lipoprotein Patterns in Animals*

	−S 40–70	−S 25–40 β globulin	−S 20–25 α_2 globulin	−S 1–15 α_1 globulin
Cat			++	+++
Dog			++	+++
Rat		+		+
Sheep		+	+	+
Opossum	+	+		+++
Monkey	+	++	+	+++
Human	+	+++	+	++
Guinea pig	+	+	+	0
Chicken	+	+	+	+
Rabbit	+	+		++
Pig		+	++	++

resistance and would be removed by the lymphatics and capillaries of the adventitia. When the intima is thickened, the lipoproteins would not pass through with facility and some of their lipid would tend to deposit. Thus the quality of the vascular filter may be a determinant of atherogenesis in the presence of normal plasma lipids.

It is easy to see that the ability to penetrate the vessel wall would also depend in part on the physical characteristics of the plasma lipids. Lipids not combined with protein have the characteristic inability to be wetted by water and would not be expected to enter or pass the endothelial cells and internal elastic membrane with ease even if they were present in plasma. The hydrophilic lipoproteins would be expected to behave oppositely. The large beta lipoproteins, heavily and unstably laden with lipid, can certainly pass through the vessel wall and appear in the lymph. But the possibility exists of their being retained in the meshes of the filter, disintegrating and shedding their lipid load which is later picked up and stored by macrophages. Without the protein to maintain its water solubility, the lipid becomes a foreign body trapped within the vessel wall.

As was to be expected, Wilens found the rate of transudation much slower through arteries than any other tissues tested. He found no evidence that some components of serum lipoproteins were more filtrable than others. Predictably, the hydrophobic neutral fats of chylomicrons were entirely unable to penetrate the walls of excised vessels.

Evans' results suggest that serum from subjects with atheroma is much more likely to deposit its lipid in excised beef blood vessels than serum from normal persons. Work of this sort is obviously important, and much more of it is needed before the mechanisms involved will be clearly defined.

Despite all the evidence of the similarity of experimental hypercholesterolemia, atherosclerosis and the human disease, it would be a grave error to assume identity. The reactions of repair and degeneration in humans differs greatly from those seen in rabbits, and there is evidence to suggest that in man they, rather than hyperlipemia, largely determine the course of the disease.

It has been said that man is unique in developing atherosclerosis. This is, however, only a relative matter. Rabbits, chickens, pigs, parrots and monkeys develop it spontaneously but probably to a lesser degree. There is a tendency for animals with large amounts of beta lipoproteins (−S 25–40) to become atherosclerotic. But certainly this alone is not enough to cause its occurrence. Dogs, cats, sheep, and rats seem to have the advantage of having no −S 40–70 fraction in their plasma, while most of the animals that develop atherosclerosis easily, do. Some animals, such as dogs, have much higher phospholipid in proportion to the cholesterol it is presumed to keep in solution; the beta lipoprotein is practically missing and the alpha lipoproteins are high.

METABOLISM OF STEROLS

I shall present only an outline of those aspects of sterol metabolism which seem apposite to the problem of atherogenesis. I realize that this part of the problem is brushed over lightly. Understanding of it is changing so rapidly that detailed analysis is hardly rewarding at the time.

The average adult consumes about 400 to 500 mg. of cholesterol a day along with a very variable amount of plant sterols. Most of the latter are poorly absorbed. The absorption of cholesterol is augmented by fat feeding, in animals at least. Most of the cholesterol is ab-

sorbed by lymphatics—for which bile is necessary—and is carried in the plasma in combination as alpha and beta lipoprotein. On normal diets, absorption is probably something of the order of 70 to 95 per cent efficient, but this is influenced by a variety of factors which have not been carefully studied in relation to atherogenesis.

Most tissues, except adult brain slices, can synthesize cholesterol, and, weight for weight, the adrenal gland seems the most efficient. Differences among species are important in the differences between hepatic and extrahepatic synthesis. Many tissues can also degrade cholesterol.

If any single organ can be singled out as most important in sterol metabolism, it is certainly the liver. For instance, much evidence suggests that the control of the level of plasma cholesterol is in the liver. It can both synthesize, probably with the participation of coenzyme A, and destroy cholesterol. The large amount contained within it has a relatively rapid turnover. Finally, cholesterol is related to the bile acid metabolism. Since much of the information has come from work on liver slices in vitro, the following outline gives examples of such observations:

1. Cholesterol is synthesized from acetate, acetoacetate, pyruvate, butyrate and stearate.
2. A parallel is found between coenzyme-A levels and the synthesis of cholesterol and total lipids in the livers of pantothenic acid-deficient rats.
3. Squalene, delta-7-cholestenol and 7-dehydrocholesterol fed to rats greatly reduce the rate of conversion of acetate to cholesterol.
4. Cholesterogenesis is reduced by hypophysectomy and by fasting in rats and is restored by glucose, protein hydrolysate and fat.
5. Cholesterogenesis is practically stopped in rats and slowed in dogs by feeding cholesterol, while fatty acid synthesis is unaffected. Neither skin nor intestinal mucosa showed a significant decrease.
6. In vitro liver extracts destroy cholesterol.

The breakdown and loss of cholesterol may occur in four ways: (a) By reduction to dihydrocholesterol directly or by passage through the intermediate cholestenone either to dihydrocholesterol or coprosterol. Both of the latter are poorly absorbed and are excreted in the feces. (b) By loss of cholesterol itself in the feces. The course of these reactions seems to be influenced by the intestinal bacterial flora. (c) By conversion of cholesterol into steroid hormones. (d) By conversion of cholesterol to bile acids by the liver.

Friedman believes the large excretion of cholesterol in bile may be used as a measure of hepatic cholesterol synthesis. So determined, hepatic synthesis in rats is depressed by estrogen and augmented by corticotropin (ACTH). Gould considers the rate of biliary cholesterol excretions more an indicator of thyroid function and the rate of metabolic activity of liver in general, rather than specifically of cholesterol synthesis.

Cholesterol esterified with a variety of fatty acids constitutes about 70 per cent of plasma cholesterol; it seems to be the more stable form of cholesterol. Where metabolic activity in diseased tissue is reduced, ester cholesterol tends to be deposited, as, for example, in atherosclerotic plaques and areas of infarction. The liver seems to be necessary for ester formation, which is surprising, since blood contains the necessary enzymatic systems for the conversion of the free to the ester form. The pancreas is believed by some to be the main source of the cholesterol esterase in rats.

When cholesterol is burned in the body, the chemical pathways followed are little understood. Chaikoff finds as much as 31 per cent of the iso-octyl side chain carbon eliminated as carbon dioxide in the expired air, while none of the ring carbon appears as carbon dioxide; rather, it was recovered in the saponifiable fraction of the fecal steroids. Liver seems to oxidize cholesterol more actively than other tissues. Intestinal bacteria play only a minor role in oxidation of cholesterol to carbon dioxide in intact rats. Cholesterol is also converted in the body, and especially in the adrenal glands, into adrenal hormones and progesterone.

There is no doubt that cholesterol synthesis and possibly destruction in the body are influenced in some species by the cholesterol in the diet, but to what degree remains to be

determined. In rabbits, however, cholesterol synthesis continues even when cholesterol feeding is prolonged and excessive.

The relative importance of the precursors of cholesterol has not been determined. Squalene seems 10 to 20 times as efficient as acetate, yet it does not produce hypercholesterolemia nor is it atherogenic. Certainly man is so richly provided with cholesterol precursors that they could hardly be withdrawn from the diet.

Lipid metabolism differs considerably in different animals, and this fact is often ignored in current literature on atherosclerosis, largely, I think, because the quantitative aspects have not been adequately studied. It is believed by many, for instance, that avian lipid metabolism differs from mammalian in being quantitatively greatly influenced by ovarian hormones.

Metabolism of Arterial Tissue

More and more data are accumulating to disprove the old conception that the blood vessels are almost without metabolism. The evidence suggests that the metabolism of vessels is not very different from that of most other tissues, especially when their heterogeneous composition is considered. Briefly, the following have been found:

1. The aortas of rabbits and chickens can oxidize acetate to carbon dioxide.

2. These vessels can convert acetate to cholesterol and fatty acids less than one-fourth as actively as can liver.

3. Calf and swine aortas are capable also of synthesizing cholesterol from acetate, the intima being the focal point of synthesis.

4. Vessel walls contain carbonic anhydrase which functions in transport of carbon dioxide.

5. Aortic tissue respires at about one-tenth the rate of liver or cardiac muscle; respiration of aortic tissue is similar in young and old rats.

6. Thyroid feeding increases the oxygen consumption and propylthiouracil decreases it.

7. About one-half of the protein in the wall of the aorta is collagen of the globular variety. The proteins, presumably muscular, differ somewhat from myosin, and the elastin differs from that in nuchal membrane.

It is possible that the metabolism of the vessel itself may constitute the key to the problem of atherogenesis; vessels may mimic an organ like the liver in becoming fatty under some circumstances and remobilizing lipid under others. The evidence does not allow me to dismiss this concept; still it cannot be viewed currently as the nub of the problem.

Enzyme Participation in Lipid Metabolism

It is an interesting fact that until very recently interest in lipid biochemistry has remained at an extraordinarily low ebb. I know because I participated in keeping it there for some years. Yet there was a good deal known in spite of its lack of integration into the other fields of chemical interest. While it has been evident that modern enzymologic methods needed to be applied to lipids, when it came it was long overdue.

All that need be mentioned here is that fatty acids are broken down to yield two carbon atom fragments which are oxidized to carbon dioxide and water by entering the tricarboxylic acid or Krebs cycle. This two-carbon atom fragment is the common denominator from carbohydrate via pyruvic acid, the amino acids and fat. This fragment is acetic acid esterified with the thiol group of coenzyme-A, i.e., $CH_3 \cdot \overset{\overset{O}{\|}}{C}—S—CoA$. Thus acetyl coenzyme-A is the "active" acetic acid. This active form opens the path to entry into the tricarboxylic acid cycle, for instance, by condensing with oxalacetate to form citrate.

Long-chain fatty acids are also activated in the same way by coenzyme-A and adenosine triphosphate, forming fatty acid esters of CoA analogous to acetyl-CoA. Through a complex series of reactions a molecule of acetyl-CoA is found, shortening the fatty acid chain by two carbon atoms.

Many of these reactions are reversible so that coenzyme-A is also involved in synthesis as well as degradation. It has already been shown to be a part of the enzymatic synthesis

of phospholipids and cholesterol. In short, the enzymatic key to the metabolism of lipids has now been found and a much more penetrating understanding of their role in atherosclerosis should follow in short order if these basic problems are not shouldered aside by the shrill demand for treatment.

The Chemical and Physical Nature of Lipoproteins

Plasma proteins contain from 3 to 5 per cent of labile lipid-protein combinations known as lipoproteins. The first one of apparently homogeneous composition was isolated by Macheboeuf from horse serum in 1929. Pedersen isolated a fraction very high in lipid by ultracentrifugation of human plasma in 1945. The long period separating these two discoveries is so typical of the field of atherosclerosis that I feel impelled to call your attention to it. Just as the alpha and beta globulins are separable by electrophoresis, so the alpha and beta lipoproteins are now separable by both ultracentrifugal and electrophoretic as well as chemical methods.

As separated from plasma, these conjugated proteins are composed of at least several amino acids and a variety of lipids. They appear to originate in the liver. Gofman believes they represent a sequence of molecules in a metabolic chain involved in the degradation and utilization of neutral fats and fatty acids. In the form of lipoproteins, the lipids are kept in a very labile and rapidly exchangeable form, ready to be taken up wherever needed.

According to ultracentrifuge studies the low-density lipoproteins are possibly divisible into molecular species with flotation rates from 2 to 40,000. The latter is familiar as the chylomicron. Cholesterol is in much greater concentration in the lipoproteins of low molecular weight and neutral fat in the high molecular weight species. Lipid may enter this system of lipoproteins in the form of high S_f lipoproteins, i.e., S_f 30 to S_f 40,000, and as neutral fat is removed by the body, the higher S_f lipoproteins give rise to successively lower members of the series.

Little is known about the nature of the proteins in the lipoproteins. This is a pity since this fraction of the molecule may determine its stability and solubility, which in turn may determine its disintegration in the vessel walls. Immunochemical methods show the lipoproteins to be constituted of a variety of different proteins, and when it is possible to separate them, antisera can be prepared for each individually, which will clarify the specific part each may play in health and disease.

The ability of the different proteins and lipids to combine and stay together (bond strength) varies greatly. Thus, Folch finds most, if not all, of the proteins present in the brain in the form of lipoproteins have widely different bond strengths. The surface of the lipoprotein molecule also must be variable. It seems to be a mosaic with commingling of areas of lipid and of peptide. In general the lipoproteins are unstable; they are unable, for example, to withstand freezing and drying without decomposing. The large amount of water in some of the lipoproteins may, to a degree, account for this instability. Clearly, knowledge of these important molecules is so limited that even speculation is restricted in value.

Nevertheless, it is clear that until many of the specific properties of the individual components of these complex molecules are understood, we should not be misled into believing that the term lipoproteins refers to closely characterized chemical entities in which the bond strength, affinities for hormones, vitamins, and other substances are presently measurable. Until such time as their specific chemical constitution is elucidated and their physical characteristics measured, clinically useful information from their study must be accepted with some reserve.

While the distinction between alpha and beta lipoproteins may at times give the impression of too great analytic precision, still there are differences which seem significant. In many diseases associated with hypercholesterolemia the beta lipoproteins are increased while the alpha lipoproteins may be either normal or low, suggesting separate mechanisms for their control. Their solubilities under various circumstances, their densities and movements in electrical fields differ.

TABLE 2.—*Movement of Lipoproteins during Ultracentrifugation at Two Densities and during Electrophoresis*

	Ultracentrifuge		Electrophoresis
Density	1.21	1.063	
Symbol	$-S_{1.21}$	S_f	
	>70	20–100+	
	40–70	10–20	β_2
Mobility	25–40	3–8	β_1
	20–25	1–3	α_2
	2–8		α_1

TABLE 3.—*Lipoprotein Pattern of Normal Human Beings*

Normal	$-S_{1.21}$ > 70	40–70	25–40 β Lipo.	20–25 α_2 Lipo.	2–8 α_1 Lipo.
Young men	22	24	180	11	154
Older men	36	33	200+	12	155
Young women	21	18	140	11	183
Older women	22	29	180	13	228

The beta lipoproteins have been studied in some detail by Oncley, Gurd and Melin. Their assumed molecular weight is 1,300,000; of this amino acid residues constitute 23 and lipid 77 per cent. Eight per cent is free cholesterol, 39 per cent ester cholesterol and 29 per cent phosphatide. This is an amazing amount of lipid for so little peptide and suggests considerable instability. The water solubility suggests that the lipids, peptides and water are arranged so that the peptides and the hydrophilic ends of the phosphatides are largely exposed on the surface of these large molecules.

Since about 70 per cent of the lipids of normal fasting human serum is in the beta fraction, these observations are of special interest. Oncley and Gurd find that beta lipoproteins react strongly with gamma globulin of human serum over a wide pH range to form a series of poorly soluble complexes.

The alpha lipoproteins contain about 2.7 times as much phospholipid per mol of cholesterol as beta lipoprotein and are smaller and more dense. Both have the same ratio of free to esterified cholesterol, approximately 1:3. The high lipid content of both the alpha and beta lipoprotein accounts for the fact that small changes in distribution of these proteins are associated with large changes in plasma lipid levels.

Lipids are the only large class of substances in the body which are insoluble in water. Their solubilizing by the device of combining loosely with protein thus becomes understandable. A few other combinations of lipids occur in the body such as the glycolipids and combinations with desoxycholic acid—the so-called "choleic acid" principle—but these are unimportant in comparison with the bulk of lipid combined in both tissue and blood as lipoprotein.

Lipoproteins Measured by Ultracentrifugation. A Word of Explanation about Terminology of Lipoproteins Measured by Ultracentrifugation

The original Gofman method used sodium chloride to obtain a density of 1.063 grams per milliliter for the flotation of the lipoproteins. The unit of flotation, Svedberg flotation unit (S_f), is one negative sedimentation unit, i.e., Svedberg unit. The Svedberg unit used in all ultracentrifugal sedimentation studies honors the inventor of the ultracentrifuge.

We believed we could increase the number of lipoproteins measurable by ultracentrifugal analysis, notably the alpha lipoproteins, by raising the density to 1.21 with potassium bromide. Changing the conditions required a change in nomenclature. The rough equivalents of Gofman's and our nomenclature are given in table 2, along with the equivalent electrophoretic patterns. We employ the symbol $-S$ to indicate negative sedimentation or flotation, with the subscript 1.21, when necessary, to indicate the chosen density.

Sex and Age

The $-S$ 25–40 fraction, which is chiefly beta lipoprotein, is normally low in females in the 18–34 age group and tends to rise with age. Beta lipoprotein in young men is almost equal to the concentration in females of 34 to 60 years of age. These facts alone suggest reasons for the vulnerability of men to atherogenesis as compared with his supposedly weaker, but far more durable counterpart, woman. Young women have much less of the

−S 40–70 fraction present than do older women. This is the Gofman S_f 10–20 atherogenic fraction.

The −S 20–25 fraction, which is chiefly $alpha_2$ lipoprotein, is present in small amount and about equal in concentration in all normal subjects. This fraction carries a number of important proteins, such as renin substrate, vitamins, such as E, tocopherol, and hormones, such as estrogen.

Women have much higher concentration of the −S 2–8 fraction, which is $alpha_1$ lipoprotein. It is this lipoprotein which has a much lower content of cholesterol than the beta lipoprotein and is presumably much more stable.

Lipoproteins and Atherosclerosis

The spectrum of lipoproteins ranging from low to high density has suggested to Gofman that this represents a sequence, in which interconversion occurs from the lower to higher density, by abstraction of neutral fat. The lipoproteins with negative sedimentation or flotation (−S) values greater than 70, with rare exceptions, contain much more neutral fat and less cholesterol than those with lower values.

The smooth degradation of lipids could be interfered with if too much lipid was put into the system or if a block existed to the ready interconversion of the different classes of lipoproteins. The degree of the block and its location in the metabolic sequence would determine which class of lipoproteins would accumulate in the blood stream.

Graham found that injected heparin progressively reduced the level of the lipoproteins of the high −S values with transitory increase and then subsequent decrease in the intermediate classes and ultimate rise in the fraction below −S 30. This progressive interconversion may continue for several hours. The most striking effect of heparin was to abolish most of the lipoprotein fraction of the class greater than −S 70.

This is not the place to give a detailed description of Gofman's fine work on the mechanism of atherogenesis. This working hypothesis of lipoprotein interconversions is a highly stimulating one, and it now remains to determine whether it is in whole, or in part, true. In essence it is his belief that a certain class of lipoproteins, i.e., those with flotation rates between 12 and 20 Svedberg units, are atherogenic. This is based chiefly on the fact that cholesterol feeding in rabbits leads to appearance of new cholesterol-bearing molecules of the class S_f 10–30 and concurrent appearance of atherosclerosis. Further, in humans, molecules in the S_f 12–20 class were found to contain approximately 30 per cent cholesterol and little protein. There was no necessary relationship between the S_f 12–20 fraction and the concentration of plasma cholesterol. The presence of these molecules was statistically related to atherogenesis.

The incidence of measurable concentrations of the S_f 12–20 fraction was significantly higher in both males and females from 20 to 40 years of age, but that in males was higher than in females. Approximately 50 per cent of the presumably normal persons of this group show appreciable concentrations of the S_f 12–20 fractions. There was a definite increase in this class of molecules in diabetics, nephrotics and patients with myocardial infarction. Restriction of cholesterol and fat reduced or even brought lipoprotein concentration to normal within two weeks to a month.

Two years later, a second class of molecules was added as significant in atherogenesis, namely the S_f 20–100. The concentration of the S_f 12–20 class is not immediately sensitive to food ingestion, while the class S_f 35–100 especially may be greatly elevated by a fat-containing meal. The inclusion of this more labile class of molecules has weakened considerably the argument as to the atherogenic specificity of the restricted S_f 12–20 class. In short, as such, they do not look nearly as pathological as they did when the original work appeared.

The core of the problem is whether these restricted classes of serum lipoproteins are, in fact, the ones which signal developing atheroma and whether they are the ones which appear in the blood vessels as atheromatous deposit. I think it fair to say that, as yet, there is no clear answer to either question.

The first of these questions is naturally one of major importance to physicians because the ultracentrifugal analysis of blood serum would warn of atherogenesis. The importance of such information could hardly be overestimated, especially since measurement of total cholesterol fails to yield correct diagnostic and prognostic information, except in the presence of persistent hyperlipemia.

Because of the importance of Gofman's observations, the National Advisory Heart Council recommended to the United States Public Health Service the organization of a carefully controlled study of the problem. Four laboratories, Berkeley (Gofman and Jones), Pittsburgh (Laufer, Hanig and Barach), Boston (Stare and Mann) and Cleveland (Lewis and Page) were designated and started work in the winter of 1950. Dr. Franklin Yeager acted constantly and effectively to keep the administration of this complex project on a level keel.

The importance of maintaining the study on as objective a basis as possible was evident. Tests were run mostly on "unknown" samples sent to all the cooperating laboratories and the results correlated in Washington by Mr. Felix Moore. More than a year was required before the centrifuge analyses and cholesterol measurements agreed sufficiently among the various laboratories. This was an important achievement and points out how difficult it would have been, had the cooperative study not been set up, to have found agreement among investigators using the ultracentrifuge. Like all new methods there were several serious "bugs" in it.

The next important point was that supposedly normal persons were examined rather than patients who had already had a myocardial infarction. The serum of a group of almost 12,000 normal people has been studied, and each year a follow up has been made to determine whether myocardial infarction or other evident vascular disease has developed.

The presence of myocardial infarction was employed to establish the diagnosis of systemic atherosclerosis because of its close association with atheromatosis and because of its relative ease of diagnosis. It is realized that mistakes can occur, but they will be overshadowed by the numbers of correct diagnoses. To eliminate error in diagnosis so far as possible, an outside committee of cardiologists, headed by Dr. Paul White, passes on the evidence of infarction submitted by the cooperating laboratories.

I suppose, after this buildup, you will expect me to give you the results. Obviously, if the experiment is to be kept objective, I cannot prejudge them. Fortunately, there is no way I can do so because the data are all sent to Mr. Moore in Washington for statistical treatment. Within the next two years it will have been gathered and the conclusions will be made known.

In place of anticipating the results, I urge you to recognize that this is an experiment, and until the results are evaluated, the original work can be neither denied nor confirmed. Any other attitude at the present time would not seem consistent with an impartial analysis.

There are, however, other aspects of the ultracentrifugal analysis of lipoproteins which are of interest and that can be reported upon. Gofman's method has certainly opened for study these substances which eventually must be significant in atherogenesis, although it is confessed at the moment that the specific application is not clear. I will, therefore, only lightly touch on some aspects that interest me.

Lipoproteins in Hypertension

This is a problem of importance to theory because of the augmenting effect of hypertension on atherogenesis. This is, of course, a loose statement, and I shall have to leave it so.

In dogs with severe hypertension of neurogenic origin, the lipoprotein pattern is unchanged, while in experimental renal hypertension the concentration of $-S$ 20–30, and especially the $-S$ 23 or alpha$_2$ lipoproteins, is increased. This shows that it is not a matter of indifference by what mechanism the hypertension is elicited. It is not surprising that hypertension in patients is associated with a variety of lipoprotein patterns.

The concentration of alpha and beta lipoproteins is normal in early hypertension of the essential variety. But as it becomes severe

or malignant, the −S 40–70, −S 25–40 and −S 20–25 classes all increase. Patients with the most severe renal disease exhibit especially great increase in −S 40–70 and >70 fractions. Developing vascular disease, atherosclerotic and/or hypertensive, especially if there is renal involvement, seems to be associated with great disturbance in the normal lipoprotein pattern of the blood. The same is true of our patients with chronic glomerulonephritis.

Nephrotic, diabetic and myxedematous patients also show abnormal lipoprotein patterns, indicating that atherogenesis is associated in a variety of diseases with increased plasma content of low density lipoproteins. These are examples of accelerated atherogenesis and do not preclude other more slowly progressive varieties, in which there is certainly no detectable change in lipoprotein pattern from supposedly normal controls.

Significance of Abnormal Lipoprotein Patterns

Currently, this is the most dangerous question I could try to answer. Still, as more and more investigation is done, there are certain guiding threads to help our thinking on the matter.

The liver, possibly the intestine as well, is involved in the synthesis of lipoproteins. What determines the relative concentrations of lipoproteins is unknown. The suggestion seems plausible that the sex hormones may have something to do with it and that the hereditary pattern is almost certainly crucial. Abnormality of one part of the plasma lipid pattern is apt to be associated with other abnormalities. Thus, patients with abnormal lipoprotein patterns often carry a greater proportion of newly absorbed cholesterol in the esterified form.

The interdependence of lipid concentrations within plasma is also illustrated in both normal and hyperlipemic sera. In disease, there may be specific deviations which are pathognomonic of the disease, such as in biliary cirrhosis, where the total beta globulin is directly proportional to the total lipids over a range of 300 to 2700 mg. per 100 cc., according to Kunkel and Ahrens. The alpha globulin showed only minor changes. More usually, all the lipids move up or down proportionately as though they were preserving an equilibrium, and this is even extended to include other substances, such, for example, as the association of blood glucose and neutral fat in diabetes.

The repeated finding of moderately elevated plasma cholesterol, with possibly a disproportionately small increase in phospholipid, after myocardial infarction, but so far not before, and in some, but by no means all patients, has not been satisfyingly explained in terms of a general mechanism of coronary atherogenesis. The danger currently seems to be to assume that the elevation of cholesterol, or for that matter, lipoproteins, preceded the infarct and was the chief cause of it. It may be, but the logic of the situation is not evident.

Table 4 shows some average figures which Dr. Lewis and I have taken from our patients to show the general deviations of the lipoprotein pattern in a variety of diseases. I would call your attention to the high beta lipoprotein in severe hypertension, the remarkably high −S >70 and −S 40–70 fractions during pyrogen treatment of malignant hypertension with low alpha lipoproteins, the excessively large $beta_1$ and $alpha_2$ fractions in nephrosis, the high −S >70 values in peripheral arteriosclerosis, the high −S 40–70 fraction in hepatic cirrhosis and the high −S >70 and −S 40–70 in familial hypercholesterolemia. The beta

TABLE 4.—*Ultracentrifuge Pattern in Disease*

	−S >70 mg. 100 ml.	40–70	25–40 β_1 Lipo.	20–25 α_2 Lipo.	10–20	1–10 α_1 Lipo.
Hypertension	50	52	250+	32		200
Pyrogen treated	180	100	180	5		40
Nephrosis	40	60	250++			120
Peripheral sclerosis	136	74	235	30		150
Cirrhosis	10	129	118	71	90	82
Familial hypercholesterolemia	95	129	266	32		112
Maternal	12	26	209	40		225
Cord	0	0	71	3		78
Lupus erythem...	78	60	169	<4		117
Multiple myeloma	59	43	59	24		95

lipoproteins are high in both poorly controlled diabetes and myxedema.

It is of interest to compare maternal with umbilical cord serum for what information it may give on the interpretation of changes in disease. Clearly the lighter lipoprotein fractions are missing in cord serum and the beta lipoproteins are about one third that in the maternal. Both alpha$_2$ and alpha$_1$ fractions are also very low.

The evidence tends to incriminate the larger and lighter lipoprotein fractions as being the ones most likely to be associated with atherosclerosis. I think the error is to believe that their presence alone is sufficient evidence to make the diagnosis of atherosclerosis and active atherogenesis. All three lighter fractions, $-S > 70$, 40–70 and 25–40, may be present in abundance without overt atherosclerosis as determined by the long-time health of individuals, yet vascular disease is far more often associated with their presence than their absence.

Table 5 shows the remarkable fact that great disturbance of the lipoprotein patterns may be present in people selected for their old age and good health. The 92 year old physician and 80 year old woman were both exceptionally vigorous and looked 30 years younger than their chronologic age. Their lipoprotein patterns are obviously bizarre in terms of youthful standards. For example, the women had a beta lipoprotein fraction almost twice normal and total cholesterol 100 mg. above the mean normal. Yet for many years these people have been in the best of health. The point I want to stress is that the blood values alone are insufficient indexes of the usefulness of the arteries.

TABLE 5.—*The Abnormal Lipoprotein Pattern of Two Vigorous Oldsters*

	$-S > 70$ mg.	40–70 mg.	25–40 (β) mg.	20–25 (α_2) mg.	2–8 (α_1) mg.	Cholesterol
92 yr. physician	30	74	294	19	259	268
80 yr. woman	71	52	317	35	141	324
Mean male normal age 35–60	60	33	>200	12	156	242
Mean female normal age 35–60	22	29	180	13	228	230

Heparin and Its Possible Participation in Atherogenesis

Most of the work on heparin stems from Hahn's observation in 1943 that injection of heparin caused the clearing of lipemic dog's plasma, while the same amount added in vitro was ineffective. Anderson and Fawcett then showed that when heparin was injected, a substance formed in blood which cleared lipemic turbidity in vitro. It was thought to be a highly surface-active heparin-phospholipid complex. Anfinsen, Boyle and Brown found the clearing factor to be a protein complex containing no free heparin but liberating ti on boiling; protamine inactivates it.

Addition of clearing factor to lipoproteins obtained from ultracentrifugation of plasma caused no clearing unless normal whole plasma was added also. The substance contained in plasma, which they called "co-protein" caused no clearing itself but was necessary for clearing to occur. The rate was proportional to the co-protein concentration when the concentration of clearing factor was held constant. Graham of Gofman's group, showed in both man and the rabbit that heparin caused a profound reorientation in the distribution of the low density lipoproteins, i.e., the lighter ones shifted to those that were smaller and heavier. According to Boyle, the S_f 20–30 class disappeared and the S_f 8–12 class appeared in the cleared sample. Heparin given to cholesterol-fed rabbits prevented the development of high concentrations of S_f 10–50 lipoproteins and retarded the development of atherosclerosis. The latter finding has not been confirmed, however, by others.

Nikkilä found a specific increase as well in the alpha$_1$ lipoproteins. Thus the lipid-rich beta lipoproteins are reduced and the lipid-poor alpha lipoproteins are increased. These reactions which seem to be enzymatic transformations may be schematized as follows:

(1) Plasma precursor protein + heparin + tissue factor → clearing factor

(2) Low density lipoproteins + plasma

coprotein clearing factor → smaller low density lipoproteins + increase in alpha$_1$ lipoproteins.

Nikkilä finds the clearing factor in post-heparin serum contained in the beta globulin fraction.

Block, Barker and Mann suggest that these principles are immediately applicable to atherogenesis since they find atherosclerotic patients fail to clear alimentary lipemia with a small dose (3 mg.) of heparin as effectively as normal people. If this observation of a relationship between atherosclerosis and resistance to clearing of lipemic plasma by heparin is established by further work, an important link between substances which could control the physical state of the plasma lipids and atherogenesis would appear to have been made. Obviously so important a conclusion should not be drawn until further evidence is available.

Most evidence suggests that the mast cells which are disposed around the blood vessels are the source of heparin. Recently it has also been shown that they contain large amounts of histamine. It is easy to jump to the conclusion that mast cells thus stand at the center of the problem of atherogenesis, and it may well be that they do, but it remains to be proved. It should also be recalled that some evidence suggests that other high molecular weight substances such as dextran sulfate have much the same effect as heparin. The rudimentary mast cell development in rabbits, as compared with rats, might be significant in the ease with which atherosclerosis is developed in the former and the difficulty with which it develops in the latter.

Nikkilä has found some decrease in protamine binding capacity of blood from atherosclerotic patients, which suggests a lowering of the concentrations of heparinoid substances. Much more searching investigations must be made before this can be accepted, as Nikkilä himself points out.

Chemical Deviations in Plasma Lipids and Atherogenesis

The weight of current evidence is in favor of some sort of chemical deviation of plasma from normal during atherogenesis. Those which have a reasonable possibility of being atherogenic follow:

1. Hypercholesterolemia.
2. Increased beta lipoprotein and decrease in alpha lipoprotein.
3. Increase in the cholesterol-phospholipid ratio.
4. Abnormally constituted lipoproteins.
5. Presence of specific atherogenic lipoproteins—Gofman S_f 12–20.
6. Hypoproteinemia and specific amino acid defects.
7. Combined protein defects and hyperlipemia.
8. Chylomicronemia.

So far, no one has found any single abnormality or combination of such which can be applied with confidence to an individual in the diagnosis of atherosclerosis. All of the abnormalities found in the chemical and physical constitution of plasma are only valid as statistical predictions in groups. For example, it is commonly stated that myocardial infarction is associated with hypercholesterolemia; this leaves one to draw the post hoc conclusion that hypercholesterolemia is the cause of the coronary sclerosis. This involves several assumptions which should, I think, be understood.

One is that the method for the determination of cholesterol is exact enough. In certain laboratories this is true. In most it is not. Another is that hypercholesterolemia preceded the infarction, although the analyses were made after! Further, it is assumed that the very mild elevation of plasma cholesterol can mean the difference between atherosclerosis and none. Lastly, scarcely more than 40 per cent of patients with myocardial infarction actually have hypercholesterolemia, and this is mostly of a very mild degree.

Blood Cholesterol Levels and Aging

Over the years there has been much conflicting testimony as to whether age alone increases plasma cholesterol levels. This has, I think, been due chiefly to failure to appreciate the full extent of the problem involved. Let us look at several facets of it.

Until very recently the error in the method for determination of cholesterol was usually great, and much greater when the technician running the method was inept. Failure of investigators to provide blind tests has been the cause of the inadequacy of much raw data, which no statistical analysis can improve. Our experience in a combined study with three other laboratories convinced us that even under the most careful control, errors can occur.

The assumption that any person "willing and able" to give a sample of blood is a "normal control" is hard to understand, particularly when most investigators in the field of atherosclerosis quite confidently state that most adults have more or less of this condition. Yet these people with more or less atherosclerosis are the normal controls. But, further, no effort has been made in most of the larger series to eliminate the obvious causes of hyperlipemia that occur in increasing numbers as people get older.

One of the most telling arguments is that in populations habitually subsisting on low-fat diets, as in Italy, Spain and parts of Africa, the serum cholesterol does not continue to rise as it does in some peoples taking high fat diets. Indeed, in some it actually falls with advancing age. From this it follows that rise in serum cholesterol is not a necessary accompaniment of aging.

Lastly, both our own work and that of Sperry show that with age, rise in cholesterol occurs in some people but not in others.

Our study was based on a study of 67 men aged 21 to 101 years, selected not at random, but from a large group with every precaution that both clinical and laboratory examination could provide to assure us that they were healthy. Measurement of the lipids was made with a gasometric method, which, while cumbersome, is not inaccurate. The analyses were run by me, chiefly, I suppose, because technicians were frowned upon in those days, but I do not think that invalidates my data. We found no consistent overall increase in plasma lipids with age. I believe that plasma lipids increase in some people, but I doubt from the current evidence that it is an obligate normal phenomenon. Most of the data published fail to consider the points I have raised.

Therefore, until the conditions for "normal" control are more adequately known and fulfilled, it seems unwise to accept the dogma that increase in age is necessarily accompanied by rise of blood cholesterol. It may well rise in some people but it always remains to be determined whether this was a normal or abnormal phenomenon.

For practical purposes, we use the following averages taken from our own data on so-called normal persons. By normal in this group is meant they had no abnormality detectable by reasonably careful pre-employment examination with subsequent annual follow-up.

	Age Group	*Average Age*	*Average Serum Cholesterol*
Females	18–35	28	207
Females	36–69	42	223
Males	18–35	29	210
Males	36–69	53	235

One other problem is of importance in this connection. Most careful investigators, notably Turner and Steiner, find the plasma lipids quite stable from day to day, and month to month. On the other hand, others have found wide variability. Whether this variability is inherent in some normal persons or is due to disease remains to be determined. Until this problem is more clearly delineated, it is well to inquire closely into the circumstances of the measurements of blood lipids before drawing sweeping conclusions.

Cholesterol-Phospholipid Ratios

Ahrens and Kunkel first suggested, in 1949, that a decrease in the amount of phospholipid in proportion to the amount of cholesterol might augment the deposition of cholesterol in the vessels; cholesterol being markedly insoluble in water, loss of the peptizing action of phospholipid would tend to allow it to precipitate. Most of the lipid phosphorus of plasma represents the choline-containing phospholipid-like lecithin. Whether other phospholipids are of equal or more importance is not known. Nor is it known just how the phospholipid functions to keep cholesterol in solution.

A not inconsiderable body of both experimental and clinical testimony supported this view. But there are many exceptions.

Wilkinson in particular believes that this ratio in arteriosclerosis does not differ significantly from the values predicted from a large miscellaneous group. Given the total cholesterol value in absence of hepatic failure, he was able to predict the phospholipid-total cholesterol ratio within narrow limits. Thus, the ratio is no more useful as an index of atherosclerosis than cholesterol itself.

Whether phospholipid in combination with the alpha and beta globulins does, in fact, aid in maintaining cholesterol in solution in plasma has not been shown, although it is certainly a reasonable suggestion. Weakening of the forces in the lipoprotein keeping the cholesterol in solution could make it more easily split off from the protein carrier and possibly deposited. The basis for the view is highly speculative and cannot at present be used to support the somewhat irregular finding of lowered phospholipids in relation to cholesterol in some patients with atherosclerosis. The problem needs much sharper definition.

The differences in various animal species are much greater than among individuals within the species. Dr. Helen Brown has summarized some of our results in table 6. We found the lipid phosphorus method to have an extreme error of ± 10 per cent but the usual is 5 per cent.

While the ratio for man shows a marked difference when compared with that of the animal studied, the animals do not arrange themselves according to the ease with which atheroma may be induced. When high fat-cholesterol diets are fed and hyperlipemia produced, the cholesterol increases well ahead of the phospholipid.

If, then, phospholipid aids in keeping cholesterol dispersed or in solution, probably as lipoprotein, then man appears inherently vulnerable because of his high cholesterol-phospholipid ratio, but he does not do so badly in comparison with animals when hyperlipemia occurs.

Distribution of Cholesterol Between Alpha and Beta Lipoproteins

Barr, Russ and Eder suggested that there may be pathogenetic significance in the distribution of lipids between the alpha and beta globulins. Using a chemical method of separation, they found that in diseases predisposing to atheroma, such as diabetes, nephrosis and xanthomatosis, relatively little of the total cholesterol is combined with the alpha lipoprotein. This implies a reduction in alpha lipoproteins and a relative increase in beta lipoproteins. Survivors of a myocardial infarct also tended to show this deviation. The abnormality may not show up in every individual but it is demonstrable in the group. I will not consider this problem in detail because Barr himself has recently ably done so in the last George Brown Memorial Lecture.

Barr has rightly pointed out that among the various criteria of lipid abnormality suggested as being atherogenic, many of the control group exhibit values well above the mean for survivors of myocardial infarction. Does this mean these supposedly normal people are themselves candidates for infarction, or does it mean that the suggested abnormality is not in fact an abnormality? Barr and Eder believe the value for distribution of cholesterol between alpha and beta lipoprotein is so far the one least likely not to show abnormality in the face of atherogenesis, but, even here, the differences between normal

TABLE 6.—*Average Cholesterol/Phospholipid Ratio in Normal Animals and Man*

	Total Cholesterol Mg. %	Lipid P mg. %	Total Cholesterol/ Lipid P
Rat	103	8.4	12
Rabbits	57	4.3	13
Dogs	149	10.6	14
Chickens	113	7.1	16
Man	235	11.0	21
Pig	129	4.6	28
Hypercholesterolemia			
Man	622	22.3	28
Rat	406	11.5	35
Rabbit	366	10.4	35
Dog	1859	39.1	48

and abnormal are small, i.e., 76 total cholesterol in beta lipoprotein as a mean control compared with 86 as a mean for survivors of infarction. They have seen patients with unequivocal evidence of atherosclerosis who did not exhibit the characteristic abnormalities in the plasma. An abnormal distribution of cholesterol between alpha and beta lipoprotein is much more liable to be significant in a young person than in a middle aged or old person. In my opinion, this work is among the most important to follow in the search for mechanisms of atherogenesis.

Chylomicrons

Chylomicrons, visible with high power and darkfield illumination, occur in large quantities in plasma after fat feeding. They are largely composed of neutral fat with little cholesterol or phospholipid. The assumption has been made by Moreton that it is the chylomicrons which are deposited in the vessel wall and produce atherosclerotic lesions. The evidence seems based chiefly on two observations: (1) Hueper's study of the atheromatous lesions produced by injection of polyvinyl alcohol, and (2) Becker, Meyer and Necheles' finding of prolonged clearing of the blood of chylomicrons in aged people. Zinn and Griffith believe that the size of the chylomicrons is fully as important as the number. I can see nothing wrong with these observations, but the evidence that chylomicrons are atherogenic is so inadequate that it is hard to understand the deference paid to the theory. Until it is supported by more testimony it can be considered as only a reasonable guess, and I feel the investigators involved would agree.

Protein Defects

Hypoproteinemia in disease is so often associated with hyperlipemia that it is reasonable to suppose some association between the two. I have supposed that the hyperlipemia of nephrosis was due to the excretion of the carrier proteins in the urine without concurrent loss of lipid. The analysis of large quantities of urinary proteins which I did a number of years ago showed almost no cholesterol or phospholipid. The kidney seemed able to split the lipoproteins and excrete the proteins while retaining the lipids.

We were unable to produce hyperlipemia in dogs fed diets sufficiently low in protein as to elicit chronic severe hypoproteinemia. Even during starvation, hyperlipemia does not usually occur. Thus, the hyperlipemia of nephrosis, as well as of some other diseases, does not seem dependent on diet but rather on metabolic disorder, which often involves protein as well as lipid.

Deficiency in the diet of the sulfur amino acids according to Mann and Stare seems greatly to augment atherogenesis in monkeys fed cholesterol, but such abnormalities would appear unlikely to occur in the diet of man.

Defect in the synthesis or degradation of the protein moiety of the lipoproteins might well be at fault. So little is currently known of the chemical and physical constitution of these large molecules which transport and keep the lipids in solution and how lipid is split off them for use in cells, that it would be unwise to assume their constant normality and efficiency. An analogous situation might be found in the study of hemoglobins which carry oxygen as the protein carries lipid. Had we sought only for abnormal amounts or kinds of oxygen, we would have been deflected from the underlying defects which occur in the carrier protein, hemoglobin. It is for such reasons I suggest the possibility that defective protein metabolism may be quite as important as defective lipid metabolism in atherogenesis.

Hyperbetalipoproteinemia

Elevation of beta globulin is so often found in severe vascular disease as to suggest some mechanistic association. But equally it may only be the reaction of the body to the disease, hence the danger of assuming a genetic association. Hypoalbuminemia is also often concurrent, as in diabetic patients with retinitis. Beta globulins are greatly increased in beta globulin plasmacytoma, hepatitis, nephrotic syndrome and some infectious diseases, hence is not a specific indicator of vascular disease.

Our own experience is chiefly with malignant hypertensives in whom there is a roughly parallel progressive rise in beta globulin with

ncreasing severity of the vascular disease. It lso rises in dogs in which the malignant yndrome has occurred during the course of enal hypertension. Such evidence cannot, of ourse, be used as direct support of the lipid oncept of atherogenesis, but as Dr. Lewis and suggested some time ago, there seems to be a oose relationship of increasing beta globulins o the necrotizing arteriolitis. While the beta globulins as measured by electrophoresis do ot necessarily parallel the beta lipoproteins as measured by ultracentrifugation, nevertheless, they often do. The beta lipoproteins being such large molecules, so heavily, and, one might say, disproportionately, laden with lipid, they could easily be conceived as providing an insecure transport of lipid across the vessel walls to extracellular fluid and lymph.

Our results, however, leave little doubt that beta globulin can be constantly above the usual normal limits for long periods of time without its having any obvious association with atherogenesis. It, like so many other parts of the mechanism, must work together to produce atheromatosis. In such a multifaceted disease, to select one facet and attribute the disease to it alone only leads to grave error.

Hyperbetaglobulinemia and Hyperbetalipoproteinemia

1. High in man and low in animals.
2. Feeding large amounts of cholesterol to susceptible animals.
3. Higher in men than young women.
4. Diabetes with retinitis.
5. Malignant hypertension.
6. Biliary cirrhosis.
7. Myxedema.
8. High in plasmacytoma, hepatitis, some infections.

Body Type and Incidence of Atherosclerosis

Body type is quite generally believed to be associated with proneness to develop coronary disease. Sprague, Gertler and Garn's work suggests that an individual with predominant muscularity, compactness and "maleness," the so-called mesomorphic type, is most likely to have an infarct under the age of 40 years. The genetic, biochemical and physiologic aspects need study along with body type to give a more complete picture of the constitutional factors. Obviously all mesomorphs do not develop myocardial infarction, and mesomorphy is hardly a remediable condition, but it is possible that diet or other measures in this group could be altered to prevent the early onset of coronary atherosclerosis. Thus body type, in addition to other criteria, may ultimately be used as a guide to those prone to myocardial infarction.

Heredity

It has been recognized for many years that atherosclerosis, particularly the coronary type, runs in families. Alvord and Adlersberg point out that patients with coronary atherosclerosis exhibit a pattern not unlike that in families with xanthoma; uncomplicated coronary disease represents a milder form of hereditary disturbance of lipid metabolism. Alvord, for instance, found that 15 members of one family had hyperlipemia, 6 had xanthoma tuberosum and 18 a history suggesting disease of the coronary arteries.

Thus idiopathic hypercholesterolemia may well be produced by a single dominant gene. Some persons carrying the dominant gene fail to exhibit hypercholesterolemia just as some fail to develop atherosclerosis or xanthelasma. Many factors are able to alter the manifestations of the main gene's effects. As Glass has forcefully pointed out, genes rarely produce absolute effects, but instead determine an individual's capacities and the nature of his reaction under specific conditions. Hereditary and environmental etiologic factors coexist and are by no means mutually exclusive.

There is a real need for investigation of the problem of atherogenesis in identical twins.

Anatomic Factors

Viewing arterial vessels as filter beds emphasizes the importance of their anatomy. The structure of the filter bed has certain fundamental differences in different species and the correlation between the anatomic variations and response to noxious agents has

yet to be carried out. Precisely the same type of correlation needs to be made within the various vascular areas in a single body. Thus a fundamental observation may lie in the fact that Duff has never seen an internal mammary artery in which atheroma was visible.

The focal and regional distribution of atheroma is familiar to you all. This distribution depends in part on the strains on the vessel imposed by its anatomy and the character of the blood flow, as, for example, at sites of branching.

One school of thought believes that hemorrhage and necrosis precede the deposition of lipid, so that the imbibition of plasma and lipid deposition is not the initiating factor. Another believes that lipid is more or less uniformly disposed throughout the intima, as a result of widespread imbibition. Early in life subendothelial fibrous zones develop and these enlarge with age. It is believed that such areas of subintimal thickening are the future sites of atherosclerosis. Dock, for instance, believes the coronary vessels of male infants exhibit this thickening, contrasting with females. Hypertension and diabetes seem to accelerate such thickening.

Wilens extends this concept to animals in which atherosclerosis can be experimentally elicited. Fibrous thickening, for example, often develops in the intima of rabbits fed cholesterol for a time, then subsequently put on a normal diet.

The internal elastic membrane may be an important barrier to the passage of lipid through the wall. Even in children splitting and intrusion of muscle occurs with eventual formation of the so-called musculoelastic hyperplastic cushions which may increase progressively in size and number. These intimal thickenings lose muscle and elastic fibers with age, becoming more collagenous. Lipid deposition in them is usually progressive.

Duff points out that in cerebral vessels most of the elastic fibers are concentrated in an unusually thick internal elastic membrane. There is no external elastic lamina and the adventitia is poorly developed. The greatest strength of the artery is in the inner layers. Early in life the internal elastic lamina begins to split with increasing duplication especially near branching of the vessel. Atherosclerosis is quite sharply limited to the intima so long as the internal lamina remains intact. Breaks in the lamina are especially frequent beneath atheroma in the intima. Duff finds that through holes so created the atheromatous contents of the lesions are squeezed out into the media. This peculiar hour glass lesion seems to be limited to the cerebral arteries and is attributable to the unusual thickness of the internal elastic membrane.

The anatomy of veins and lymphatics is such that atherosclerosis is extremely rare. The thin walls without elastic lamella probably interpose too feeble a barrier to allow much lipid to remain in the wall during filtration.

Detection of Atherosclerosis

The answer to the problem of the clinical recognition of latent atherosclerosis is simple; we have no way. No problem in the field more urgently needs an answer.

Coronary atherogenesis can proceed undetected to an extreme degree. Despite the altogether too facile use of the term, cerebral arteriosclerosis, or atherosclerosis, it also remains undetectable until after death. It is a harsh thing to say, but it needs saying; there is no reliable way to make the diagnosis of cerebral or coronary atherosclerosis.

Without methods for measurement of the presence and progress of atherogenesis, study of treatment becomes practically impossible. Doubtless much of the current looseness of talk and thought in the advertising of presumed antiatherogenic agents depends on this.

Diet

Since feeding of large amounts of cholesterol results in experimental atherosclerosis in some animal species, and some of the cholesterol fed is found actually in the atherosclerotic plaques, it is understandable that dietary cholesterol has long been suspect as the chief offender in atherogenesis.

Keys' recent work has provided convincing statistical evidence that populations consuming low-fat, low-caloric diets have low serum cholesterol values and that these do not in-

crease with age. Where the diets are high in fats and calories, as in America, England and Denmark, serum cholesterol levels considerably exceed those in such low-fat consuming countries as Italy, Spain and parts of Africa.

Most investigators now agree that it is the amount of fat rather than the cholesterol consumed which is crucial in the effect of diet on blood cholesterol; this is in marked contrast to the results of fat and cholesterol feeding in animals. A few years ago, based on cholesterol feeding experiments in rabbits, reduction of dietary cholesterol alone was thought to be the key to the problem of reducing blood cholesterol. But it has been known for many years that cholesterol feeding in man produces little or no change in plasma cholesterol. So far, no one has found any direct relationship between cholesterol content of diet and plasma cholesterol. The basic concern is with fat, not cholesterol. Probably it does not matter either whether vegetable or animal fat is given. I think many of us had hoped that vegetable fat would not have the same effect as animal, but this proved an illusion.

Four years ago I studied the problem in myself, chiefly I think, because my serum cholesterol was about 300 mg. and my "abnormally" elevated S_f 10–20 lipoproteins were certainly two strikes against me. At first I reduced the fat content of my diet to about 15 per cent of the total calories, making up the loss with carbohydrate. There ensued a sharp fall in plasma lipid, sharp loss of body weight, an impairment of my disposition and a contraction of my circle of friends. During this period of several months, gastrointestinal disturbance was marked, but worse was the feeling of depression and irritability. Addition of vegetable fat quickly overcame both but simultaneously raised serum cholesterol and beta lipoprotein. I was unable to find any decisive influence of protein. The experiment was ended after a year, with the firm conviction that diets should be changed with the greatest caution, and that physicians should be required to try their diets before prescribing them. Subsequently, I have for three years voluntarily kept my lipid intake at approximately half the level of five years ago, and while this effectively keeps my waistline down, it has no effect on blood lipids. It is of course absurd to draw conclusions from one example; the experience has merely aided me in evaluating conclusions drawn from statistical studies on the effects of diet on the blood lipids in terms of the individual.

Steiner, for example, found little coronary disease among Okinawans who were undernourished, eating predominantly a diet of rice and potatoes, and obtaining protein mainly from soybean and fish. On the other hand, Corcoran did not find the serum cholesterol of Eskimos abnormal although they ate heavily of meat and fat and were not undernourished. Obviously, there are important factors other than diet which determine atherogenesis. As Sprague pointed out, many people have consumed from 60,000 to 100,000 eggs in their lifetime without acquiring lethal atherosclerosis.

I would like to re-emphasize that individual responses to diet may differ greatly. I published a striking example several years ago, comparing the lipoprotein and total cholesterol response to a variety of dietary overloads with cholesterol and fat. The lipids moved up or down in one patient, mirroring faithfully the dietary fat changes; in the other, a middle aged atherosclerotic, they could not be budged by the most drastic changes. Some persons are highly sensitive to dietary lipid changes; others are not. It reminds me of the high or low sensitivity of some people to coffee or gin.

Since the evidence points strongly to an association between high fat intake and increased serum lipid, the question must be answered: what sort of diet could be substituted? It is pretty well agreed that in animals too drastic reduction of fat with substitution of carbohydrate for calories ultimately leads to fatty degeneration of livers and kidneys. Possibly this is due to loss of essential unsaturated fatty acids. Further, rats fed diets in which less than 10 per cent of the calories are furnished by fat, early exhibited changes in composition of body lipid suggestive of ageing. Dogs require not less than 16 per cent of the calories as fat and more than 1 per cent of the calories as unsaturated fatty acid for

survival. For these and other reasons, it is clear that a diet in which less than 15 per cent of the total calories are supplied by fat is dangerous. Whether diets higher in fat, but still low according to the ordinary standards in the United States, will maintain a lower average serum lipid, remains to be determined. If the answer involves almost lipid starvation to achieve "normal" serum lipids, then the problem seems to me an almost insoluble one in terms of diet.

Most evidence so far has not demonstrated any difference in responses to the kind of fat given. Recent work by Kinsell and his associates has thrown some doubt on this in that they found the intake of large amounts of vegetable fat compatible with decrease of serum cholesterol esters and phospholipids. Substitution of vegetable fat for animal fat in diabetic diets high in protein and fat resulted in major fall in levels of cholesterol and phospholipids. Opposite results in normal people were found by Hildreth. This is another example of the conflicting evidence on this aspect of the problem of atherogenesis and the need for caution in drawing too sweeping conclusions until some of the conflicts are resolved.

Inheritance and/or disease often may be a much more important factor in setting the level of plasma lipid than diet. Farr and I were unable to alter significantly the hyperlipemia of nephrosis by wide changes in the dietary lipid intake. Changes as great as from 5 to 64 per cent of the total calories supplied by fat left the blood lipids unaffected. Wilkinson has convincing evidence that the hyperlipemia of essential familial hypercholesterolemia has no relationship to the absolute amounts of carbohydrate, protein, fat or cholesterol in the diet. The increased blood cholesterol seems to be endogenous, not dietary.

On the other hand, a number of observers have found that a low-fat diet (20 Gm. fat) quite consistently reduces blood lipids after two to four months in familial xanthomatosis. Such diets have been tried after myocardial infarction but the results are still equivocal, and they are likely to be until the most rigid type of experiment is set up; too many variables are inherent in the problem to allow solution by easy and superficial methods. The rice diet which is by its nature low in fat and cholesterol reduces especially plasma cholesterol esters in hypertension with little change in free cholesterol or phospholipid; it is uncertain that this is sustained after body weight comes to equilibrium. The lipoprotein, especially the S_f 10–20 fraction, seems to be unaltered by the rice diet according to Kendall, while neutral fat is considerably elevated.

Weight loss significantly reduces the lipoproteins as measured by ultracentrifugal analysis and total cholesterol as well, especially if the values are initially high. Stare and his associates find that in subjects with initial lower levels, weight loss elicits no decrease, or decrease followed by rebound, or even increase. The degree of initial obesity is not a determining factor.

Great increase in total calories even with very low lipid intakes undoubtedly tends to raise the lipid content of the blood. Caloric balance as well as total lipid intake thus are important in the control of levels of plasma lipids.

As Chandler, Lawry, Potee and Mann have found, when a strong positive caloric balance is maintained with a fat-free diet, all of the lipoproteins increase. Change in lipoproteins can be produced either by reducing dietary fat or by altering caloric balance.

The relationship to obesity is not clear. Gofman and Jones found the S_f 35–100 class moderately related and the S_f 12–20 less so.

Thus, about the most to be said is that diets should be moderate in calories and that one fourth of the total calories may be furnished by lipid. Extremes of lipid restriction potentially can do more harm than good, but excess fat intake after youth should be avoided.

Diet and Atherogenesis

1. The body can synthesize 2 Gm. of cholesterol a day to be compared with the usual intake of 0.2 to 0.4 Gm. a day; the cholesterol content of the diet is therefore less important because of endogenous synthesis.

2. People on low fat diets have lower plasma lipids.

3. The fat, not the cholesterol content, is important.

4. The total caloric intake is important.

5. Vegetable and animal fats seem equivalent.

6. The level of blood lipid in some individuals, and possibly races is largely independent of diet.

7. The hyperlipemia of most diseases is endogenous.

8. Moderate caloric intake with one quarter as fat, seems reasonable.

9. Extremes of fat intake should be avoided.

Measures Other than Diet which Affect Blood Lipids

It is a hope that agents will be found which consistently and harmlessly reduce hyperlipemia and/or inhibit atherogenesis. While the search has been limited in scope, nothing of practical value has turned up. On the other hand, some promising leads have been uncovered. The following summarizes the scanty knowledge of the measures, other than diet, which lower plasma lipids.

1. Thyroid and iodide feeding, estrogen injection, corticotropin (ACTH) in dogs.

2. Dihydrocholesterol, phytosterols and brain extract feeding.

3. Soya lecithin (temporary) reduces cholesterol.

4. Inanition (stress?)

5. Heparin.

6. Ultraviolet irradiation, oxygen (?)

Iodine. Thyroid substance and sodium iodide depress plasma lipids. Iodide has been traditional in the treatment of arteriosclerosis, although its value was never proved. It has fallen into disrepute. The following evidence suggests the part played by iodide and thyroid in atherogenesis.

1. Both inorganic iodide and thyroid substance inhibit experimental hypercholesterolemia and atherosclerosis in rabbits and chickens.

2. Plasma cholesterol increases in hypothyroidism and decreases in hyperthyroidism.

3. Cholesterol content of plasma is not correlated with basal metabolic rate.

4. Basal metabolic rate and antiatherogenesis are not correlated.

5. Administered iodide causes a butanol-insoluble protein-bound iodine to appear in blood and tissues. This fraction possibly is associated with antiatherogenesis.

6. Iodide may affect the receptivity of vessel walls which determines the amount of lipid deposited and the reactivity which determines the tissue response to the lipid.

Unfortunately, large doses of iodide are required in most animals to prevent the experimental disease. This might suggest that similar large doses would be required in human beings, but this does not follow. We seldom attain the overwhelming lipemia elicited by the abnormal conditions imposed upon the experimental animal. The hyperlipemia to be inhibited is often minimal.

There may be other actions of iodide than abolishing hyperlipemia. Some evidence suggests that the receptivity and response of the blood vessel wall to lipids may be affected by iodide. By receptivity I mean the ability of the tissue to retain lipids, whether in or out of foam cells. By response I mean the new vascularization of the area, the response of fibroblasts and ground substance of the vessel, and finally the total tissue response to the deposited lipids: a very broad concept indeed, but one that does, I think, have much to recommend it for the guidance of research.

In both normal and thyroidectomized rabbits, iodide in large doses reduces hepatic cholesterol. Even after cholesterol feeding, iodide prevents the usual rise in liver and blood. Iodide seems to have rather more effect on exogenous than endogenous hypercholesterolemia since, for instance, the endogenous hypercholesterolemia resulting from thyroidectomy is unaffected by iodide, as is that of nephrosis. Both animals and man fed iodide show increase in plasma inorganic and protein-bound iodide in proportion to the iodide dosage. Curiously, thyroidectomized animals show a greater response than do normal ones.

Fractionation of the protein-bound iodine shows a butanol-soluble, alkali-insoluble part which contains the active thyroxin of the blood. This shows little increase after iodide

feeding. Most of the increase in protein-bound iodine is contained in the butanol-insoluble residue.

Increase in plasma content of this butanol-insoluble fraction and inhibition of hypercholesterolemia in rabbits fed cholesterol run in parallel, which led Brown and me to suggest that by association this fraction of protein-bound iodine was concerned in cholesterol metabolism. Its formation seems to be largely independent of the thyroid gland, more of it in fact being produced in thyroidectomized animals than in normal ones on the same dose of iodine. The difficulty with this concept is that it does not account, so far, for the effectiveness of thyroxin in preventing atherogenesis.

The oral iodide dosage required to produce measurable concentrations of serum butanol-insoluble iodide was small in rabbits and dogs, larger in rats and man; the daily dosage being of the order of 0.4 mg. iodine per kilogram for rabbits and 8 to 14 mg. for man. Hypothyroid animals required roughly one-tenth the minimum dosage to elicit the same response. The maximum attainable concentrations appeared in rabbits at an iodide dosage of 16 mg. per kilogram; in rats at more than 20 and in man at 31 to 41 mg. Clearly these dose schedules require comparatively large amounts of iodide if they are to be used as a means of preventing atherosclerosis. Poor as current understanding is, iodide administration is still the most effective antiatherogenic method known today in the cholesterol-fed rabbit.

Thyroid substance also reduces hyperlipemia but this action is limited by its effect on basal metabolism. The effects on lipid metabolism are not well understood. In patients with nephrosis, amounts sufficient to raise basal metabolic rates as high as +50 have little effect on the plasma lipid levels.

The association of hypothyroidism and hypercholesterolemia in both animals and man is well recognized, as is also the disappearance of the lipemia following thyroxin administration. Further, depression of the gland with thiouracil, at least in cholesterol-fed dogs, augments atherogenesis. This led to the belief that the thyroid function is in some manner causally associated with development of atherosclerosis.

Blumgart, however, found an average increase in blood cholesterol level of 125 mg. above the pretreatment level in totally thyroidectomized patients maintained at levels of hypothyroidism at approximately −20 per cent basal metabolic rate. In the course of 1 to 13 years these patients did not develop unusual atherosclerosis. Under these circumstances, it is questionable whether the hypothyroid state with its hypercholesterolemia is by itself a sufficient cause for the production of coronary atherosclerosis.

A few scattered facts from laboratory experiments are known. Thyroxin increases, and thyroidectomy decreases, the incorporation of deuterium into the cholesterol in liver, intestine, kidney and spleen. Apparently the mean half-life of cholesterol is short (7 days) in hyperthyroid rats, 20 days in normal and 50 in hypothyroid animals. Far more cholesterol is excreted in the bile of hyperthyroid rats than in normal ones and only about half as much as normal in hypothyroid ones, according to Friedman. Hyperlipemia induced by stilbestrol is only partially inhibited by thyroid in chicks, emphasizing what seems to be a lesser effect of thyroid on endogenous lipemia.

Thyroxin and 2, 4-dinitrophenol, two agents that greatly increase cellular metabolism, although probably by quite different mechanisms, failed to hasten the regression of well developed lesions in rabbits. 2, 4-Dinitrophenol in nontoxic doses also did not influence the development of experimental atherosclerosis. Thyroid is partially inhibitory in chicks and strongly so in rabbits. Clearly the effect on oxygen consumption per se is not concerned in antiatherogenesis. Probably for the same reason the concentration of cholesterol in blood is not directly correlated with the degree of thyroid deficiency or hyperactivity.

The effect of iodide is dependent on the dosage employed. Low doses often elicit hypercholesterolemia and rise in hepatic cholesterol, which is opposite to the effects of larger doses. Much remains to be learned about this interesting phenomenon.

Estrogens. Studies on estrogens made several

years ago showed them to cause hyperlipemia. Among the most potent was stilbestrol, which elicited severe lipemia even on a fat-poor diet. Subsequently, a variety of results have been obtained. Some observers find depression of total serum cholesterol, others find no effect, in part, possibly, depending on dosage and mode of administration. Probably the best evidence, both from the laboratory and clinic, shows some fall in cholesterol and elevation of lipid phosphorus, hence depression of the cholesterol-lipid phosphorus ratio. A fall in serum beta lipoproteins has been observed in some patients. Barr and Eder found administration of estrogens to male survivors of myocardial infarction resulted in an increase in alpha and decrease in beta lipoproteins. Katz and Stamler are convinced that estrogens inhibit coronary atherogenesis in cockerels fed a cholesterol-containing diet, and that this effect is associated with decreased cholesterol-lipid phosphorus ratios. Curiously, estrogen failed to exert any prophylactic effect against atherosclerosis of the aorta in any of the birds. So far there is no convincing evidence that estrogens are of any clinical value in prophylaxis or treatment; unfortunately antiatherogenesis and feminization parallel one another in the various estrogenic molecules according to Eder.

Testosterone may have some of the properties of an estrogen antagonist. In castrate rabbits, at least as Lewis, Masson and I found, its administration causes the appearance of abnormal lipoprotein peaks, $-S > 70$ and $-S$ 40–70, in the ultracentrifuge pattern. This conversion of the sexually immature animal to one with greater "maleness" may have significance in relation to the greater susceptibility of males to atherosclerosis.

Effect of Plant Sterols and Brain Extracts on the Absorption of Cholesterol. Recently there has been a flurry of papers suggesting that the feeding of phytosterols prevents absorption of cholesterol. Peterson in 1951 found soybean lipid, which contains beta sitosterol, prevented atherosclerosis in cholesterol-fed chickens. Dihydrocholesterol behaved similarly in both rabbits and man according to some observers, but others have failed to confirm this for either sitosterol or dihydrocholesterol in either man or rat. Much more work is obviously required.

Structural analogs such as cholesteryl chloride are believed to increase fecal excretion of ingested cholesterol, so lowering blood cholesterol.

The approach is an interesting one but so far has nothing to recommend it in prevention or treatment of atherosclerosis.

Succinylsulfathiazole, which inhibits growth of the coli group of organisms in the gut, inhibits coprosterol formation. Twelve years ago Rosenheim showed that extracts of brain contain a factor essential for conversion of cholesterol into coprosterol. Since cholestenone was found in the feces of rats fed brain extract, the view that cholestenone is an intermediate in the conversion of cholesterol into coprosterol was strengthened. From this work it seemed possible that sufficient cholesterol might somehow be converted to the nonabsorbable coprosterol to lower the cholesterol level of the blood. Recently Jones fed a cholesterol-free, lipid-poor residue of beef brain (40 Gm. per day) to patients with arteriosclerotic heart disease and showed reduction of serum cholesterol in three of the six patients. The work must be greatly furthered before its importance can be evaluated.

Lecithin and Starvation. Soya bean lecithin has enjoyed a vogue as a presumed prophylactic against atherosclerosis. The testimony supporting such an attribution carries little weight. Adlersberg showed that feeding 15 Gm. or more a day may cause in some people a fall in serum cholesterol, but on continued feeding, the cholesterol returns to its original level. The fall is of the order of 15 or more milligrams.

Starvation in both man and animals greatly reduces plasma cholesterol, especially the ester fraction. Some experimental evidence suggests that partial reversal of atherosclerosis in animals may be so induced. I will only mention the quite substantial evidence that in some nations subjected during the war to near starvation, the incidence of myocardial infarction and generalized atherosclerosis fell to unusually low levels.

Adenosine 5-monophosphate, according to Milch, administered to cholesterol-fed cockerels

elicits a pronounced fall in serum cholesterol and possibly beta globulin. The mechanism is not understood.

Treatment of Atherosclerosis

Properly speaking, there is no treatment of atherosclerosis. There may be ways of slowing its development; it is possible there are ways of aiding its resolution, but there are no practical ways of preventing it or curing it as judged by experiments in animals. I stress the adjective, "practical," because it is obvious that the conditions under which atherogenesis is elicited experimentally are so abnormal that its prevention implies imposition of an equally abnormal state.

I think it wiser to view the current proposals for treatment largely as tentative thrusts into the unknown, some capable of being built upon, most too weak to support a superstructure. Below I list some of these worthy, in my opinion, of further investigation.

Methods of Antiatherogenesis with Suggestive Evidence in Their Support

1. Iodide and thyroid administration.
2. Low caloric-low fat diet.
3. Heparin-like substances.
4. Estrogens.
5. Dihydrocholesterol and other cholesterol analogs.
6. Brain extracts.
7. Active exercise with its massaging action on lymph flow.

The recent realization that atherosclerosis is, from the numerical point of view, the greatest cause of death is beginning to be reflected in the commercial side of medicine. The large consumption of dairy products by adults in those countries with high incidence of atherosclerosis is causing many to wonder if this is a sound nutritional program. Unfortunately, the dairy industry has done little to provide an answer to the problem. Like the tobacco industry, they have waited until the disaster of uncertainty is well upon us and them.

Another reflection of the growing awareness of the problem by commerce is the appearance on the market of a variety of mixtures of lipotropic substance with vitamins, minerals and rutin; none are of proved value and few have even any semblance of experimental evidence to support their use as a treatment or prophylactic in atherosclerosis. Their recommendation is based on the philosophy that they do no harm and might do good. This is an expensive and elusive philosophy, seldom contributing to the advancement of sound therapeutics, and greatly contributing to logical delinquency in the minds of the prescribing physician. It mirrors mechanized medicine at its worst.

The claims made in some cases have been so preposterous and so full of double talk that I feel impelled to give you an example or two. "The . . . formula provides rational prophylaxis and therapy in interrelated degenerative disorders affecting hepatic and vascular function among middle aged and elderly patients." ". . . containing the lipotropic factors choline, inositol, ethanolamine and essential fatty acids, as they occur naturally, has shown a much higher degree of lipotropic effectiveness than synthetic or isolated forms and represents, therefore, the ideal lipotropic preparation in the management of disorders involving impaired fat metabolism, such as atherosclerosis, coronary artery disease, hypercholesterolemia, diabetes, liver insufficiency . . ." This does not differ fundamentally from a modern perfume advertisement which states, "Keyed to contemporary living—new concepts of space, freedom of motion and freedom of spirit . . . show Fourth Dimension is definitely the perfume for today's woman—agelessly young, and unlimited in possibilities! Wearing an aura of Fourth Dimension around you will be a rewarding experience." I am quite prepared to believe the latter is true, if expensive. But I am far from convinced that our remedies for atherosclerosis are either "keyed to contemporary living"—"new concepts of space, freedom of motion and freedom of spirit," or will keep you, "agelessly young, and unlimited in possibilities." That they are "unlimited in possibilities" there is no doubt.

I point to these absurdities to emphasize the need for clear and penetrating thinking, especially in the clinical investigation of atherosclero-

sis and the need for intelligent dollars and investigation at least in part by those who will eventually so richly profit by sound discoveries in the treatment and prevention of atheromatosis.

What I have had to say may sound negativistic—no methods for detection, no treatment—but it is true. It is the price of neglect. The rich background of fundamental knowledge is simply not there on which to draw. Until this deficit is remedied on a very broad base, it is unlikely that the current shocking death rate from coronary and cerebrovascular atherosclerosis will be greatly altered except as it will be influenced by improvements in treatment of hypertension. Iodism, starvation, castration and parent selection are not inherently appealing or practical measures.

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Development of Hypertensive Manifestations after the Disappearance of Hypertension

By GEORGE A. PERERA, M.D.

The accelerated ("malignant") phase of hypertensive vascular disease is more common in men; sympathectomy may modify some of its signs and symptoms even in those cases in which hypertension is not modified. Six instances are reported herewith in which patients in the accelerated phase have developed retinopathy and papilledema during a sustained period of normal blood pressure brought on by a vascular accident or sympathectomy. Therefore factors other than the intensity of the hypertension may be involved in the pathogenesis of this phase.

IN HYPERTENSIVE patients, events such as myocardial infarction, cerebral vascular accidents or bilateral thoracolumbar sympathectomy may be followed by periods of normal blood pressure for weeks or even months. During such a period of reduced blood pressure, occlusive phenomena, changes in heart size, or alterations in renal function may occur, yet the underlying mechanisms cannot be interpreted with certainty; they may result from the pre-existing organic disease or be the sequel to a drop in arterial tension or to differences in cardiac function. On the other hand, progression of retinal lesions during this period of sustained normal blood pressure may throw some light on the processes involved—at least on those pertaining to the production of retinopathy.

In six instances (three after a myocardial infarction, one after a cerebral thrombosis, two after sympathectomy) papilledema and retinopathy have been observed to appear during a normotensive period when they had been absent prior to the hypertensive phase. Examination of the ocular fundi was made through dilated pupils by a single observer, with at least three observations before the episode, and one observation two or more weeks after, during which interval no hemorrhages, exudates or papilledema were visualized. All of these patients had documented hypertensive vascular disease with subsequent proteinuria; none of them had evident complicating or intracranial disease; on clinical grounds they were all in the early accelerated phase of their disease; and, following these observations, two have died with confirmation of the diagnosis of the accelerated phase with necrotizing arteriolitis.

A case report will serve as an illustrative example:

Eight years ago, J. B., a 43 year old Negro janitor, came to the hospital complaining of frequent occipital headaches. His blood pressure at that time was recorded as 176/110. Three urinalyses were negative. There was no evidence of intracranial or endocrine disease, nor was there evidence of coarctation of the aorta. Four years later an intravenous pyelogram disclosed no abnormalities, and one year before the present observations a benzodioxane test disclosed a normal, mild pressor response. Throughout the eight-year period of observation, repeated blood pressure readings were recorded and varied from 170/100 to 226/126. The eyegrounds showed mild, then moderate arteriosclerotic vessel changes only, but for several years urinalyses disclosed a mild proteinuria together with hyaline casts and occasional red blood cells. After eight years of known hypertensive disease and without antecedent cardiac signs or symptoms, he developed the characteristic pain pattern of a myocardial infarction and was admitted to the medical wards of the Presbyterian Hospital. The diagnosis was confirmed by the appearance of fever, leukocytosis, elevation of erythrocyte sedimentation rate, and typical serial electrocardiographic changes consistent with a posterior wall infarction. The patient's course was complicated by a day of mild shock, and the disappearance of hypertension throughout a hospital stay of 38 days. Daily casual blood pressure readings during the first 10 days and measurements twice

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weekly thereafter, varied from an initial 96/50 to a maximum value of 138/86. There were no signs of congestive failure, no arrhythmias, and no signs or symptoms of encephalopathy or cerebral vascular disease. The cardiac silhouette was moderately enlarged by X-ray examination and three urinalyses in the course of this admission disclosed a constant 2 plus proteinuria with specific gravities never above 1.016. The blood urea nitrogen concentration was 18 mg. per 100 cc.

On admission the eyegrounds revealed only moderate arteriosclerotic changes in the retinal vessels, and the funduscopic picture was similar 11 and 19 days after the date of admission. On the twenty-fourth day of his hospital stay (blood pressure 126/80), bilateral retinal hemorrhages and blurring of the nasal disc margins were noted for the first time, progressing to the point of definite papilledema within a space of one week. Although complaining of blurred vision, he refused further assistance, was discharged still with a normal blood pressure, and died eight months later of congestive failure and uremia following admission to another hospital.

Autopsy, including examination of the brain, disclosed cardiac hypertrophy, a healed myocardial infarction, extensive necrotizing arteriolitis, nephrosclerosis, and no signs of intracranial disease.

Discussion

It has been suggested that the mechanism of the accelerated ("malignant") phase of hypertensive vascular disease is closely related to blood pressure levels, particularly to increases above some critical level for each patient, and that neuroretinal edema is due to raised intracranial pressure, a consequence of the high level of diastolic arterial pressure.[1] There is no doubt that levels of the arterial tension are generally higher in those in this stage of the disease than in those in less advanced stages, and that sodium-restricted regimens, drugs or surgical procedures which lower the blood pressure are associated usually with regression of retinopathy. However, the accelerated phase may develop at times with only slight to moderate increases in blood pressure. Furthermore, cerebrospinal fluid pressures within the normal range have been encountered in some hypertensive patients with papilledema and retinopathy in this clinic, and consequently the appearance of papilledema and retinopathy in the absence of hypertension in six instances observed by us poses further questions regarding the mechanisms involved.

If a complication, for example, papilledema, can develop weeks after the disappearance of hypertension, at least in the accelerated phase, consideration must be given to possible causative factors other than those related only to arteriolar vasoconstriction. Thus it would appear that the blood pressure lowering effects of agents and procedures employed in the management of hypertensive disease may be only a partial reason for their usefulness. At any rate, the rare but definite appearance of retinopathy and papilledema, after a hypertensive patient has lost his hypertension, indicates that high diastolic values are not solely responsible for their development. These observations support the view that at least some manifestations of the accelerated phase of hypertensive vascular disease may be related to something more than the intensity of the hypertension.

Conclusions

1. Six instances have been encountered in which patients with the accelerated ("malignant") phase of hypertensive vascular disease have developed retinopathy and papilledema during a sustained period of normal blood pressure.

2. Factors other than the intensity of the hypertension may be involved in the pathogenesis of the accelerated phase.

Sumario Español

La fase acelerada ("maligna") de la enfermedad hipertensa vascular es mas común en los varones; la simpatectomía puede modificar algunos de los hallazgos y síntomas aún en los casos en los cuales la hipertensión no sea modificada. Seis casos en la fase acelerada se informan, en los cuales se desarrollo retinopatía y papiledema durante un período sostenido de presión arterial normal causado por accidente vascular o simpatectomía. De manera que hay otros factores además de la intensidad de la hipertensión que pueden estar relacionados a la patogénesis de esta fase.

REFERENCE

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Serum Lipoprotein Stability in Atherosclerosis

By Louis Horlick, M.D.

The alpha toxin of *Clostridium welchii* is a potent lecithinase which disrupts the serum lipoproteins, eventually resulting in complete separation of the lipids from the protein fraction. This reaction is associated with the development of turbidity, the intensity of which is related to the quantitative level of serum lipids. The time of onset of turbidity, however, appears to relate to the stability of the serum lipoprotein bond. Individuals with coronary disease showed early development of turbidity and high final turbidity in 64 per cent as compared with 14 per cent in a control group and 6 per cent in a group of young normal subjects.

THERE is evidence to suggest that the physicochemical state of the serum lipoproteins may have an important bearing on the genesis and progression of atherosclerosis in man and animals.[1a, b, c, 2a, b] It has been demonstrated by chemical fractionation technics that there is a characteristic pattern in the distribution of the lipids among the different protein fractions, and that there are differences in pattern on the basis of sex, age, and the presence of abnormal conditions, such as atherosclerosis, diabetes, nephrosis and hypothyroidism.[1a, b, c] In atherosclerosis, more of the cholesterol is carried in the beta lipoprotein fraction where the ratio of phospholipid to cholesterol is low.[16] It may be assumed that the β lipoprotein is more amenable to deposition in the subintimal tissues, or "less stable" than the alpha lipoprotein. Gofman and his associates have demonstrated that several classes of sharply defined lipoproteins (characterized ultracentrifugally) are associated with atherosclerosis in man and animals.[2a, b] Again, these classes of molecules (S_f 10–100) may be considered less stable than those from S_f 0–10.

Another measure of the "stability" of the serum lipoproteins has been the serum cholesterol-phospholipid ratio, that is the ratio of hydrophobic to hydrophilic lipids. Boyd was the first to show that turbidity could be found in sera of normal lipid content where the ratio between the lipids was grossly disturbed in favour of the hydrophobic lipids.[3] The turbidity was due to the formation of aggregates of poorly emulsified fat particles. Ahrens and Kunkel confirmed Boyd's work, and also demonstrated that by the enzymatic destruction of serum lecithin they could render previously clear sera turbid.[4, 5] Numerous observers[6, 7, 8] have since reported that a relatively high cholesterol-phospholipid ratio is found in individuals with atherosclerosis and in experimental animals fed cholesterol.[9, 10, 11] The converse, namely, that a low cholesterol-phospholipid ratio tends to protect against the development of atherosclerosis, has been demonstrated in animal experiments with such diverse substances as Tween,[12] alloxan,[13] cortisone[14] and stilbestrol.[15]

Estimation of the stability or solubility of serum lipoproteins may inferentially provide a method for estimating the susceptibility of individuals to atherosclerosis. Although the serum lipoproteins constitute only one factor in a very complex interaction of serum and tissue factors, yet measurements of lipoprotein stability may serve to detect individuals with disorders of lipid transport and isolate them for further study. The methods employed to date are cumbersome and time consuming and do not lend themselves to mass application. The method which we have developed and

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hich is described below is simple and rapid d may be useful in clinical work.

Historical Introduction to Method

In 1939, Nagler observed that when *Clos-idium welchii* was grown in human serum, palescence developed and eventually a layer f fat rose to the surface. This reaction was pecific for *Cl. welchii* and was inhibited by *Cl. welchii* antitoxin.[16] Macfarlane and co-workers studied the reaction further and noted that a large number of refractile fat globules could be seen under darkground illumination during the course of development of turbidity. Their chemical studies revealed that the course of the reaction ran parallel with the breakdown of serum lecithin to phosphorylcholine and a diglyceride, and they were able to follow its progress by measuring the amount of water soluble phosphorus set free. They concluded that the alpha toxin of *Cl. welchii* was a highly specific lecithinase, and that the appearance of turbidity must be due to the breakdown of lipid-protein complexes which occurred when the stabilizing effect of lecithin was removed.[17] Further work by Macfarlane[18] demonstrated that sphingomyelin, too, could be hydrolyzed by the *Cl. Welchii* toxin, and that other members of the Clostridia could elaborate toxins which gave the Nagler Reaction.[19]

In 1946, Petermann[20] studied the effect of *Cl. welchii* lecithinase on human serum globulins using electrophoretic and ultracentrifugal technics. She noted complete disappearance of the "X protein" (or massed lipoproteins) from the serum following incubation with lecithinase, and in addition a decrease of 13 per cent in the β_1 boundary in the electrophoretic diagram. The lipid material separated off carried with it 5 to 10 per cent of the total nitrogen. This confirmed previous studies by Crook[21] who had demonstrated that the material separated consisted of one third protein, and two thirds fat (fat, cholesterol, phosphatides, etc.).

Studies with purified serum protein fractions[20] demonstrated that the enzyme attacked β_1 globulin lipoproteins found in fraction III-1 of the serum proteins with the production of intense turbidity. Very little turbidity was produced when the enzyme was incubated with fraction IV-1 (albumin, α_1, α_2 and some β). This would suggest that the beta globulin lipoproteins are perhaps more susceptible to breakdown by the enzyme and that they contribute the lion's share of the turbidity produced by the enzyme.

Both Nagler[16] and Crook[21] noted that sera varied in their sensitivity to lecithinase (that is, some developed turbidity sooner than others when incubated with lecithinase). Crook also noted that this variation in end points was quite wide.

More recently the Nagler reaction has been restudied by Ahrens and Kunkel,[4] and by Zamecnik and associates.[22] The former investigators noted that when serum was incubated with lecithinase, considerable enzymatic destruction of lecithin could be demonstrated prior to the development of mensurable increases in optical density of the serum. They also noted that the final turbidity of the lecithinase-treated serum correlated reasonably well with the total lipid content of the serum as determined chemically. Zamecnik and colleagues[22] have carefully investigated and described the enzyme kinetics of the interaction between lecithinase and lecithin.

Our interest was aroused by the finding of Ahrens and Kunkel[4] of the correlation between turbidity and total lipid content of the serum. This study was repeated using both normal individuals and individuals with coronary atherosclerosis and their findings were confirmed. During the course of this work it became apparent that turbidity appeared to develop earlier in the sera of individuals with coronary disease than in normal controls. It was decided to investigate this further, and to this end an attempt was made to standardize a lecithinase preparation so that a comparable amount of enzyme would be added to each serum tested. With this standardized toxin, groups of young normal persons, middle-aged and elderly normal persons, and individuals convalescent from coronary disease have been investigated. The results suggest that there is a distinct difference between normals and individuals with atherosclerosis in the response of their serum to incubation with lecithinase, and

we believe that this is a reflection of the degree of stability of their serum lipoproteins.

Materials and Methods

Materials

1. *Cl. welchii* lecithinase* in fluid and dried state was used. The material contained principally α toxin. Zamecnik and co-workers[22] had assayed similar material from the same source and had found it to contain in addition a small amount of θ toxin and approximately 2000 mucin clot prevention units of hyaluronidase per milliliter. The dry toxin was prepared by saturation of the toxic filtrate with ammonium sulfate. The toxin was assayed by Lederle Laboratories using the mouse subcutaneous half lethal dose test, at from 350 to 600 minimal lethal doses (mld.) per milliliter.

Liquid toxin was diluted with borate buffer diluent immediately prior to use. The usual dilution was 100 times. Powdered lecithinase was dissolved in borate buffer diluent to make a 0.025 per cent solution. Fresh solutions were made up at least once a month and were stored in the refrigerator.

2. Lecithin was prepared from egg yolks by ether extraction and acetone precipitation following the technic of Macfarlane and Knight.[17] A 2.5 per cent solution in distilled water was used. It soon became apparent that there might be differences in the lecithin obtained from different batches of eggs. To obviate this difficulty a large amount of lecithin was prepared by Pangborn's method,[24] which yields a purer product, and stored in vacuum-sealed ampules in the refrigerator.

3. Borate buffer was prepared as described by Adams.[23] It contained: boric acid 12.5 Gm., sodium chloride 8.12 Gm., calcium chloride 1.12 Gm., gelatin 5 Gm. and Merthiolate 0.1 Gm. per liter. Its pH was adjusted to 7.2 which is the optimum for the enzyme. The calcium content serves to accelerate the enzyme reaction, and the gelatin serves to prevent inactivation of the enzyme by shaking and dilution.

Methods

(a) *Serum Lipid Determinations.* All sera studied were subjected to lipid analysis. In all, except the young control group, venous blood was drawn before breakfast, and complete lipid analysis was done. In the young control subjects blood was drawn one to two hours after breakfast, and only serum cholesterol was determined. Cholesterol was determined by Sperry and Webb's modification of the Schoenheimer-Sperry method[25]; lipid phosphorus by Youngburg's method as modified by Hawk, Oser and Summerson[26] and neutral fat by the method of Man and Gildea.[27]

(b) *Enzyme Standardization.* Standardization of the enzyme preparations was carried out as described by Macfarlane and Knight.[17] One ml. of a 2.5 per cent lecithin solution was added to 3 ml. of buffer in thin-walled glass tubes in a water bath at 37 C. To this was added 1 ml. of enzyme solution, and the mixture incubated for 15 minutes. The reaction was stopped by adding 1 ml. of 20 per cent trichloracetic acid. The solution was filtered from the flocculated lecithin within 15 minutes through no. 43 Whatman paper and refiltered until clear. In the blank tubes, the trichloracetic acid was added before placing them in the water bath. Total phosphate was determined on 1 ml. aliquots of filtrate by Youngburg's method.

Macfarlane has defined an enzyme or lecithinase unit as the amount releasing 0.1 mg. phosphorus from excess lecithin at pH 7.6 and 37 C.

(c) *Lecithinase Turbidity Test.* In our early work we followed the technique described by Ahrens and Kunkel.[4] Two-tenths ml. of serum was added to 1 ml. of borate buffer containing 10 mld. of toxin and readings were made at 0, 1, and 2 hours, using the Evelyn microcolorimeter attachment and filter 620. Later on, when we became interested in observing the "lag period" and time at which turbidity first appeared, we employed 0.5 ml. of serum, 0.16 ml. of lecithinase solution (0.5 lecithinase unit) and 5.34 ml. of buffer (total volume 6 ml.). Readings were made at half hour intervals using the Evelyn colorimeter and filter 620. Galvanometer readings were converted to density readings (L = 2 log G). These were multiplied by 100 to give "turbidity units." An increase of three units from the first reading was taken to indicate the point of first development of turbidity. In most cases this occurred at the same time that turbidity could first be made out by the eye. Turbidity readings were recorded at 24, 48 and 72 hours. The 72 hour reading was adopted as final turbidity point.

Clinical Material

Two groups of normal individuals, one young (mean age 22.1 years) and one older (mean age 50.2 years.), and a group of individuals with coronary disease (mean age 57.7 years) were investigated. The composition of the groups is shown in table 1. Normal individuals were selected on the basis of lack of complaints referable to the cardiovascular system, and a normal physical examination. In some instances they were in hospital for surgical procedures, but most of them were seen in the course of routine annual health examinations in an industrial medical service. Individuals with coronary disease were selected from patients hospitalized with bona fide myocardial infarction as judged by clinical and

* Supplied through the courtesy of Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

TABLE 1.—*Composition of the Groups Studied*

Group	Total Number in Group	Males	Females	Average Age		
				Range	Mean	S.D.
Coronary...	50	40	10	35–79	57.65	±12.1
Old control.	50	42	8	35–78	50.22	±11.65
Young control.....	131	65	66	16–34.5	22.11	±4.59

electrocardiographic evidence.* Blood was drawn at least three weeks after infarction. Individuals with diabetes or hypertension or with a history of liver disease were excluded. Turbidity tests and serum lipid determinations were carried out on all sera.

RESULTS

1. *Enzyme Assays*

Standardization of the lecithinase proved to be a difficult problem because of the impossibility of securing a standard lecithin substrate. Using lecithin prepared from egg yolks by the method of Macfarlane and Knight,[17] it soon became obvious that the results of enzyme assays were variable within fairly wide limits. Pure lecithin is commercially unobtainable. It has been prepared synthetically by Baer[28] in forms in which the constituent fatty acids are known and constant, but we were unable to obtain enough of this product to carry out standardization procedures. Fairly pure lecithin was prepared by Pangborn's method,[24] and was stored in evacuated ampules in the refrigerator. Table 2 demonstrates the results obtained with seven solutions of enzyme, made up between April 2, 1953 and Oct. 14, 1953. The standardization values obtained on Aug. 9, 1953 show a modest variation between samples. The retest on Oct. 26, 1953 (two and one half months later) shows lower values for the solutions dating from April to July, and only slight change in the solution of Aug. 8, 1953. The solutions of September 18 and October 14 are well within the range obtained with the other solutions on August 9th.

TABLE 2.—*Standardization of Lecithinase Enzyme (0.025 per cent)*

Lecithinase Solution	Egg lecithin solution (2.5%)		
	Aug. 3/53	Aug. 9/53	Oct. 26/53
	mg. P released from excess lecithin in 15 min. at 37 C. by 1 ml. lecithinase		
No. 1 (April 2/53).....	0.2454	0.2220	0.1818
No. 2 (April 27/53).....	0.2658	0.2370	0.1920
No. 3 (June 11/53).....	0.2658	0.2352	0.1944
No. 4 (July 16/53).....	0.2454	0.2112	0.1878
No. 5 (August 8/53).....		0.2190	0.1992
No. 6 (Sept. 18/53).....			0.2190
No. 7 (Oct. 14/53).....			0.2112

2. *Characteristics of the Lecithinase Reaction.*

(A) In figure 1 the time course of the development of turbidity against the amount of water-soluble phosphorus released in the course of the reaction has been charted. It will be noted that there is a lag period varying between two and four hours during which the major amount of hydrolysis of lecithin occurs, but which is characterized by no essential change in turbidity. Immediately following this period there is a very marked increase in turbidity with only slight changes in the amount of water-soluble phosphorus released.

In serum G which is from an individual with coronary atherosclerosis there is an earlier onset of turbidity (that is, a shorter lag period) than in serum F which is from a control, two and one half hours against four and one half hours. In addition, the final turbidity attained is in excess of 80 units for G as compared with about 65 in F.

The higher final turbidity readings in G are taken to indicate the greater amount of unstable lipoprotein present in this serum as compared to F. These values correlate fairly well with the actual serum lipid values, as will be shown below.

(B) Attempts have been made to arrest the reaction at various time intervals so that the reaction products could be examined more closely. *Cl. welchii* antitoxin or potassium

* From the wards of the Royal Victoria Hospital, and Queen Mary Veterans Hospital, Montreal, Canada.

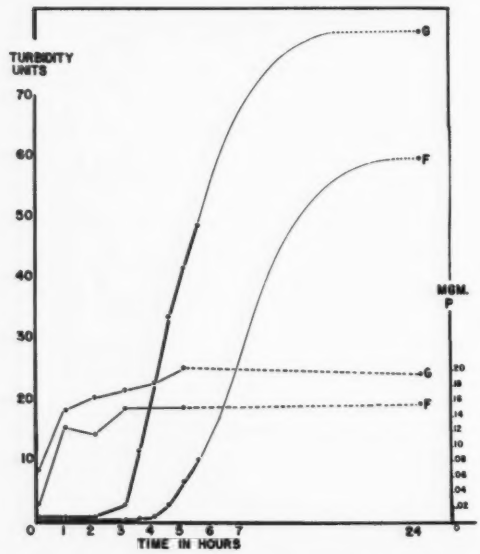


FIG. 1. Relationship of breakdown of lecithin to development of turbidity in serum incubated with lecithinase at 37 C. Breakdown of lecithin is followed by determination of water soluble phosphorus liberated. Serum G is from a patient with myocardial infarction, serum F is from a normal individual. Discussion in text.

oxalate* will inhibit the Nagler reaction when added to serum before exposure to lecithinase. If serum is exposed to lecithinase for a period which varies from 5 to 20 minutes the Nagler reaction can no longer be inhibited by antitoxin or potassium oxalate. By the addition of potassium oxalate at intervals of 1, 2, 5, 10, 20 minutes of the mixing serum and enzyme, the reaction was arrested after varying degrees of turbidity had developed. The sera were subjected to paper electrophoresis[29] and stains for protein (0.1 per cent bromphenol blue) and lipoprotein (Sudan black) were carried out. Figure 2 shows a representative sample. In the normal control serum sample the lipoproteins are concentrated in the α_1 and beta bands. Exposure of the lipoproteins to enzyme for one minute followed by addition of oxalate results in striking changes in the protein and lipoprotein patterns. The α_1 globulin band disappears from its expected position, and the α_2 and beta globulin bands show considerable retardation in their migration rate. The albumin and gamma globulin show no change from the control. Immediately ahead of the α_2 is an indistinct band which might be α_1. There is complete disappearance of the α_1 lipoprotein band and a single band is now seen parallel with the α_2 globulin band. It trails a diffuse Sudan staining deposit all the way to the line of origin. Exposure of the lipoproteins to enzyme for 24 hours, without addition of oxalate, results in no further changes in the protein pattern, but markedly

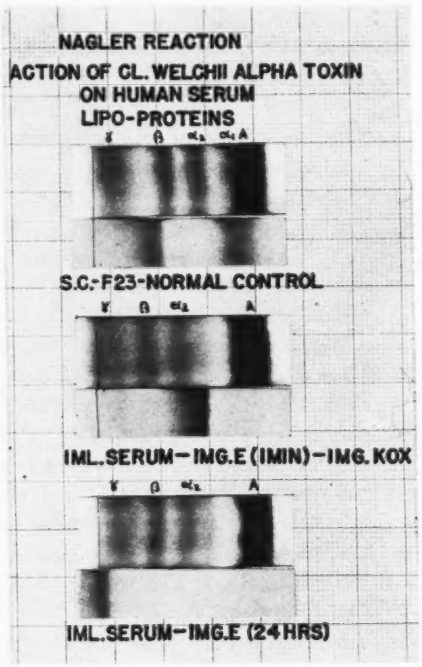


FIG. 2. Paper electrophoresis of serum from a normal young female age 23. Upper paper stained for protein (0.1 per cent bromphenol blue), lower paper stained for lipid (Sudan black). The top pair of papers are the untreated controls. The middle pair represent the serum after exposure to enzyme for 1 minute followed by addition of potassium oxalate and further incubation for 24 hours, and the bottom pair represent serum in which no oxalate was added (i.e. no attempt was made to slow down the reaction). For discussion see text.

* I am indebted to Dr. J. H. Quastel of the Montreal General Hospital Research Institute for the idea of using oxalate to retard the lecithinase reaction.

modifies the lipoprotein pattern. All the lipid staining material remains at the line of origin (fig. 2).

It is of interest that despite the marked change in the distribution of the lipoproteins in the sample exposed to enzyme for one minute, the serum was quite translucent, whereas longer exposure resulted in grossly turbid sera. It appears, therefore, that the lecithinase enzyme alters the α_1-β lipoproteins, probably producing new classes of lipoproteins of altered mobility, and releasing a considerable amount of lipid from the protein binding. If the reaction is permitted to go to completion, there is a complete release of all the lipid material from protein linkage, and it remains as a single band at the point of origin, together with a variable quantity of protein.

3. *Variability of Lecithinase Test Data*

(*a*) *Reproducibility of Results Using Identical Serum and Lecithinase Solutions, and Repeating Tests on Different Days.* Results obtained with samples of serum from three patients are shown in table 3. In all instances there was good agreement between the data obtained when tests were repeated at intervals of from two to eight days.

(*b*) *Reproducibility of Results Using Identical Serum Samples but Different Lecithinase Preparations.* Results of five sera tested with lecithinase solutions, one of which was three weeks old, and the other two days old, are given in table 4.

There is a moderately good agreement between the two sets of data. There is a variation of a maximum of one hour in onset of turbidity in one serum, one-half hour in three, and no variation in one. Final turbidity readings show only a very narrow range of variation (range 1 to 3.2 units, average 2.3 units).

(*c*) *Reproducibility of Results on Retest of Individuals at Varying Time Intervals, Using Different Lecithinase Solutions.* Data are available on eight patients, and are shown in table 5. The maximum variation in time of onset

TABLE 3.—*Variability of Lecithinase Test Results. A. Identical Serum and Enzyme*

Serum	Date	Time of onset of turbidity in hours	Final turbidity units
(1) Ab	(1) Aug. 14/53	6	69.9
	(2) Aug. 22/53	5.5+	67.8
(2) Br	(1) Sept. 25/53	3	58.5
	(2) Oct. 3/53	3.5	64.3
(3) Ma	(1) Sept. 25/53	3.5	
	(2) Oct. 3/53	4.0	

TABLE 4.—*Variability of Lecithinase Test Results. B. Identical Serum with Different Enzyme Preparations*

Serum	Enzyme Solution 1 (July 16/53)		Enzyme Solution 2 (Aug. 8/53)	
	Time of onset of turbidity in hours	Final turbidity units	Time of onset of turbidity in hours	Final turbidity units
Hoo	5	55.7	6	58.9
Hor	5	60.2	5.5	62.9
Co	5	48.8	5.0	49.8
St	5	69.4	4.5	72.1
La	4	63.8	3.5	65.8

TABLE 5.—*Variability of Lecithinase Test Results. C. Same Individuals Retested at Intervals of from 1 to 10 Months*

Serum	Date	Time of onset of turbidity in hours	Final turbidity units
Ho	Jan. 31/53	5.5+	63.8
	Mar. 20/53	6.0	58.5
	Aug. 8/53	5.0	60.2
La	Jan. 31/53	4.0	68.8
	Aug. 8/53	4.0	63.8
Gr	Jan. 31/53	3.5	84.6
	June 14/53	3.0	87.0
	July 16/53	4.5	92.1
Hoo	Mar. 20/53	4.5	56.1
	Aug. 8/53	5.0	55.7
Well	June 14/53	3.5	67.8
	July 16/53	4.5	71.0
Lep	May 22/53	8.0+	48.5
	June 13/53	9.5+	48.5
Dio	Mar. 3/53	4.5	44.4
	Mar. 20/53	4.5	62.9
Ad	Dec. 20/52	4.0	62.9
	Jan. 31/53	3.5	65.8

of turbidity ranges from 0 to one and one-half hours, with most cases showing a variation of one half hour. It is unfortunate that more data were not available on this crucial point. Two of the cases (Gr and Well) tested "normal" on one occasion and "coronary" on another on the "onset" criterion. There was good agreement in final turbidity readings in all except one case (Di).

Summary. There is little variation in results when the same enzyme solution and serum sample are retested at intervals up to eight days. Using different enzyme preparations the results are a little more variable and this may be due to the fact that standardization of the enzyme is not yet sufficiently accurate. Retests at intervals of months on the same individuals show relatively little change in the final turbidity readings, but a somewhat wider variation in time of onset of turbidity, which may be due to spontaneous changes in the physicochemical pattern of the serum lipoproteins.

4. *Results of Lecithinase Test*

(A) Time of onset of turbidity in all sera tested is shown in figure 3. The earliest appearance of turbidity was at less than two hours after the beginning of the reaction, and the latest at 48+ hours. Examination of the data for the coronary and older control groups reveals a distinct difference in the time of onset of turbidity in these groups. If a line is drawn between the 4 and 4.5 hour readings, 36 (72 per cent) of the 50 coronary patients fall on one side of it, and 39 (78 per cent) of the 50 controls on the other. In the younger control group 34 out of 123 cases (21 per cent) demonstrated turbidity before the 4.5 hour mark.

In some instances readings were not made until four hours after the beginning of the reaction. Sera from eight patients with coronary disease showed considerable turbidity at the time of this first reading, and it may be assumed that the onset of turbidity was prior to the four hour reading in all of them. In other instances readings were taken for 4.5, 5, 5.5 and 6 hours only, and in these runs, many sera had not yet become turbid when the final readings were made. It may be assumed that the true onset of turbidity in these cases, numbering four coronary patients, three older controls and 75 younger controls would have been later than shown in the figure 3. Because of these factors it is impossible to calculate the true mean values for the time of onset of turbidity in the three groups studied.

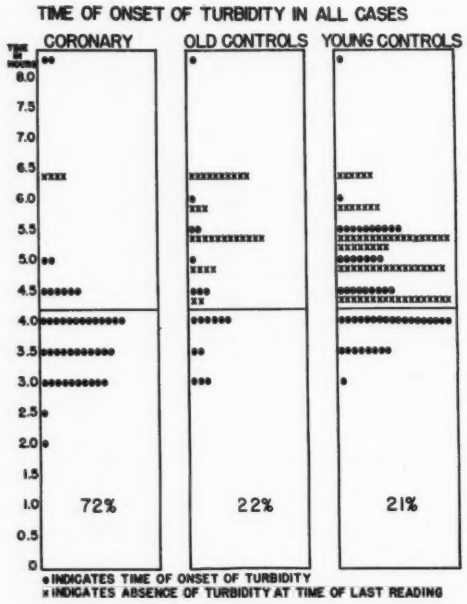


FIG. 3. Time of onset of turbidity in all cases in the three groups studied. The line drawn between 4 and 4.5 hours separates the cases in which turbidity occurred early (below the line) from those in which it occurred later.

(B) *Final Turbidity Readings.* In table 6 we have compared the range of turbidity readings, mean values and standard deviations of final turbidity values in the three groups studied. There is a significant difference ($p = 0.05$) between the coronary and the older control group. There is a much greater difference ($p > .001$) between the young control group, and the two other groups.

When a turbidity reading of 60 units is selected (a value which corresponds roughly to about 250 mg. per 100 cc. cholesterol), 72 per cent of the coronary group, 54 per cent of the older control group, and 13 per cent of the young controls exceed this value.

(C) *Relationship of Time of Onset of Tur-*

TABLE 6.—*Summary Table of Final Turbidity Values*

	Coronary Group	Old Controls	Young Controls
Mean	67.55	60.99	50.23
S.D.	±13.15	±12.00	±10.28
S.E.	1.88	1.71	0.90
p*		0.05	>0.001

* Probability of significant difference from coronary group

bidity to Final Turbidity Readings. In figure 4 the relationship of the final turbidity readings to the time of onset of turbidity (using only the cases where the latter value was precisely established) is shown. Since many cases were not followed beyond 4.5 hours the figure is heavily weighed by those cases in which turbidity occurred early. There is a very wide range of turbidity readings for each time interval, but there appears to be a linear relationship between time of onset of initial turbidity and final turbidity values in the time zone between 3 and 5.5 hours. Beyond 5.5 hours the data suggest that the relationship no longer holds.

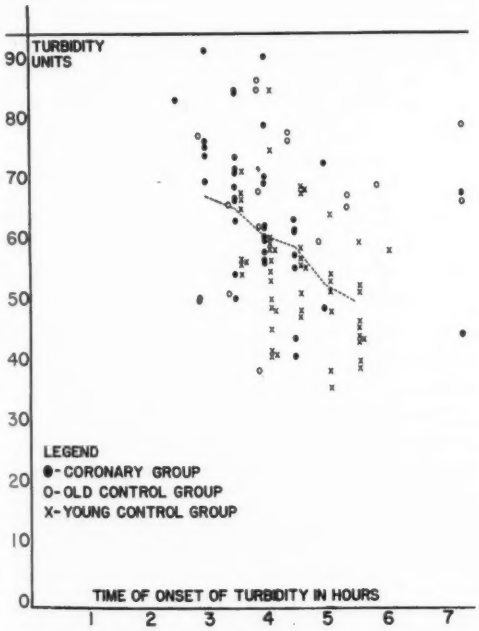


FIG. 4. Relationship of time of onset of turbidity to final turbidity. Dotted line is the mean of all the turbidity values at each time interval.

TABLE 7.—*Correlation of Serum Lipid Fractions with Final Turbidity Reading*

	Coronary Group	Old Control Group	Young Control Group
	r	r	r
Total cholesterol	0.61	0.61	0.58
Free cholesterol	0.36	0.75	0.39
Ester cholesterol	0.50	0.57	0.41
Lipid phosphorus	0.75	0.78	
Fatty acids of neutral fat	0.51	0.18	
C/P molar ratio	−0.05	0.16	

(D) *Relationship of Final Turbidity to Serum Lipid Fractions.* The mean values and statistical analysis of the serum lipid fractions in the three groups studied are shown in table 10. Comparing the coronary and older control groups, it is apparent that there is a statistically significant difference in the free and total cholesterol and lipid phosphorus. All the lipid fractions are significantly lower in the young control group as compared with the other groups.

Correlations between the final turbidity and the individual lipid fractions have been calculated for the three groups and are shown in table 7. Similar values were obtained for "cholesterol" in all three groups (r = 0.61, 0.61, 0.58). High correlation values were also obtained for lipid phosphorus in the coronary and older control groups (r = 0.75 and 0.78). In the older control group, the free cholesterol showed a higher degree of correlation (0.75) than in any of the other groups.

5. *Discriminatory Ability of the Lecithinase Test*

In table 8 the data for the three groups studied have been arranged to show the percentage of cases with early development of turbidity and high final turbidity in each group. It is noted that both of these factors coincide in a much greater percentage of cases in the coronary group as compared to the older control group (64 per cent against 14 per cent). Using both criteria, the degree of discrimination is better than that for either one alone.

In table 9 the diagnostic findings in the cases in the younger and older control groups which showed both early onset of turbidity and high final turbidity have been listed. In

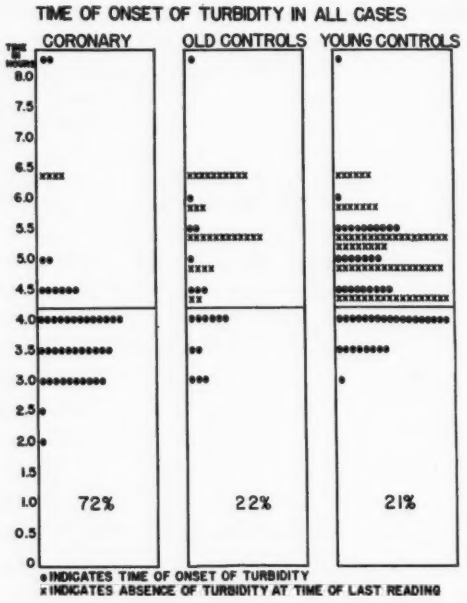
of turbidity ranges from 0 to one and one-half hours, with most cases showing a variation of one half hour. It is unfortunate that more data were not available on this crucial point. Two of the cases (Gr and Well) tested "normal" on one occasion and "coronary" on another on the "onset" criterion. There was good agreement in final turbidity readings in all except one case (Di).

Summary. There is little variation in results when the same enzyme solution and serum sample are retested at intervals up to eight days. Using different enzyme preparations the results are a little more variable and this may be due to the fact that standardization of the enzyme is not yet sufficiently accurate. Retests at intervals of months on the same individuals show relatively little change in the final turbidity readings, but a somewhat wider variation in time of onset of turbidity, which may be due to spontaneous changes in the physicochemical pattern of the serum lipoproteins.

4. *Results of Lecithinase Test*

(A) Time of onset of turbidity in all sera tested is shown in figure 3. The earliest appearance of turbidity was at less than two hours after the beginning of the reaction, and the latest at 48+ hours. Examination of the data for the coronary and older control groups reveals a distinct difference in the time of onset of turbidity in these groups. If a line is drawn between the 4 and 4.5 hour readings, 36 (72 per cent) of the 50 coronary patients fall on one side of it, and 39 (78 per cent) of the 50 controls on the other. In the younger control group 34 out of 123 cases (21 per cent) demonstrated turbidity before the 4.5 hour mark.

In some instances readings were not made until four hours after the beginning of the reaction. Sera from eight patients with coronary disease showed considerable turbidity at the time of this first reading, and it may be assumed that the onset of turbidity was prior to the four hour reading in all of them. In other instances readings were taken for 4.5, 5, 5.5 and 6 hours only, and in these runs, many sera had not yet become turbid when the final readings were made. It may be assumed that the true onset of turbidity in these cases, numbering four coronary patients, three older controls and 75 younger controls would have been later than shown in the figure 3. Because of these factors it is impossible to calculate the true mean values for the time of onset of turbidity in the three groups studied.



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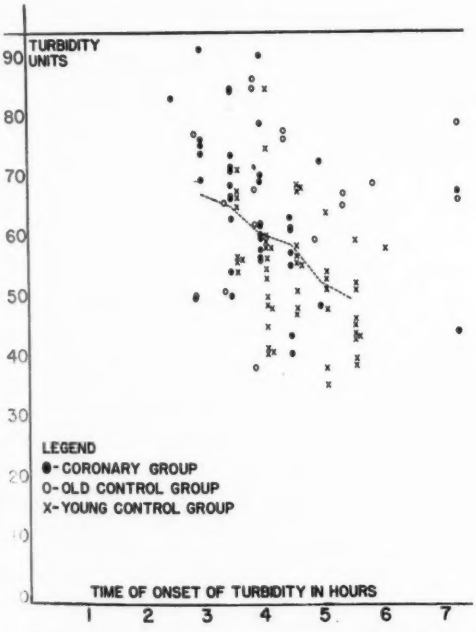

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In table 9 the diagnostic findings in the cases in the younger and older control groups which showed both early onset of turbidity and high final turbidity have been listed. In

TABLE 8.—*Summary of Turbidity Test Results in All Cases*

Group	No. in Group	Time of onset of turbidity <4.5 hrs.	Final turbidity >60 units	Both criteria
		%	%	%
Coronary.....	50	72	72	64
Older controls..	50	22	54	14
Young controls.	131	21	13	6

TABLE 9.—*Clinical Features of Cases in Both Control Series Showing High Indexes*

Name	Sex	Age	Clinical Features	LT	T. O. T.
Tre	M	44	Foot deformity, BP 140/100	62.9	4.0
Ker	M	61	G.I. investign., phychosis, BP 150/100	77.6	3.0
Kel	F	37	Para I. periodic examination	63.8	<4.0
Sml	M	47	Periodic examination	68.8	4.0
Dav	M	43	Periodic eaamination	87.0	4.0
Hay	F	39	Periodic examination	66.3	3.5
Cha	M	69	Hemorrhoids	85.4	4.0
Ros	M	22	Postop. appendicitis	61.1	4.0
Eag	M	33	Periodic examination	85.4	4.0
Len	F	19	Obesity	60.2	4.0
Von	M	26	Obesity (+22 lbs)	67.3	3.5
Ben	M	20	Obesity (+5 lbs)	68.3	3.5
Duf	F	22	Normal—pre-employment	65.8	3.5
Bed	M	26	Obesity (+10 lbs	75.7	4.0
Buj	M	32	Avitaminosis, ex P.O.W.	72.0	3.5

the older control group, two of the cases had borderline diastolic pressures (100 mm. Hg), and of the remaining five, four were clinically normal, and one was hospitalized for hemorrhoidectomy. In the young control group, only two individuals were unequivocally normal, four suffered from varying degrees of obesity, one had been a prisoner of war and had suffered from avitaminosis, and one was recovering from appendicitis. In the normal series there were 16 individuals who were classified as obese. Four fulfilled both criteria of the test, three showed high final turbidity only and one early onset of turbidity only. Thus the obese young people gave more positive tests than did those of normal weight, on a relative basis. Whereas the young normal series was evenly divided on the basis of sex, six out of the eight cases which fulfilled both criteria were males. Failure of 36 per cent of the coronary patients to give a positive test may be due to the following.

1. In a very small proportion of cases of myocardial infarction etiologic factors other than atherosclerosis are responsible.

2. Lipid levels in individuals with coronary disease are known to be much more variable than in normals.[30] The episodic character of the serum lipoprotein changes may explain the failure of positive tests to be obtained in some cases, and the variability of some of the cases on retest.

3. The etiology of atherosclerosis is as yet far from certain. We must admit the possibility of etiologic factors other than lipid instability in atherosclerosis, in the present state of our knowledge.

DISCUSSION

The lecithinase of *Cl. welchii* toxin alters the lipoproteins of serum, breaking up the complex molecules of lipid and protein, and releasing the lipid. In the course of this reaction new classes of lipoproteins appear which differ in mobility from the pre-existing ones. The work of Petermann[20] suggested that the β globulin lipoproteins were selectively attacked by lecithinase. The point of attack is most likely the lecithin in this complex molecule, and the breakdown of the lecithin may loosen the bonds holding the complex molecule together, resulting in changes in molecular shape and volume. Such changes, together with the coalescence of free lipid droplets may be responsible for the resultant turbidity. At any rate, the appearance of turbidity may be taken as an indication of profound changes in the physicochemical structure of the serum lipoproteins. It is contended that the early occurrence of such changes in some sera after exposure to lecithinase, is an index to the fact that the lipoproteins are unstable in vivo. Where the lipoproteins are more stable, longer

periods of exposure to the enzyme are required to break up the lipoprotein complex. In figure 1 it has been shown that this is not related to the rate of breakdown of the lecithin (as measured by release of phosphorus). Despite relatively similar rates of hydrolysis of lecithin, one serum became turbid in half of the time required for the second. There must therefore be other forces at work, which resist the disruptive tendencies of the lecithinase. It is also possible that only certain classes of lipoproteins can be attacked by the enzyme, that is, there may be some molecules where the lecithin is exposed by virtue of the internal structure of the molecule. The latter possibility suggests that the early appearance of turbidity may be related to the presence of unusually large amounts of such lipoprotein classes.

The fact that the early development of turbidity occurred in 72 per cent of a group with coronary arteriosclerosis as compared with 22 per cent and 21 per cent of the older and younger control groups respectively would suggest that in the coronary group, the lipoproteins are most amenable to disruption by lecithinase and possibly less stable than in the control groups. It is of interest that there was no real difference in the percentage of individuals with early onset of turbidity between the older and younger control groups despite a considerable difference in mean age of the two groups. It is well known that the atherogenic process begins early in life and progresses for many years. It is not surprising, therefore, that a relatively high percentage of young people show evidence of "unstable lipoproteins."

Early development of turbidity appears to be related in part to the degree of final turbidity which will develop in the serum after 72 hours. Since final turbidity correlates well with the levels of the serum lipids determined chemically, early turbidity is sometimes an index to grossly disturbed serum lipid levels. This is not always true, and in the present series there are many instances where turbidity developed early in the presence of normal serum lipid levels. The relationship may merely be due to the fact that the lipids are being carried in certain lipoprotein classes which are especially amenable to attack by the enzyme.

The relationship between final turbidity and the serum lipid fractions have been shown in table 7. The only conclusions that can be drawn from these data are that the final turbidity correlates in a general way with serum lipid levels, and can be used as an index in gross disturbances of serum lipid levels. Our data on the serum lipid fractions are in general agreement with those published by other investigators.[6, 7, 8] The difference in the total cholesterol values between the coronary and control groups is largely accounted for by the free cholesterol. This is not in agreement with most workers who have found the difference mainly in the ester fraction.[6, 7, 8] We were unable to discern any difference in the cholesterol-phospholipid molar ratio between the two groups, and between them and the young control group.

The two criteria discussed above, (early onset of turbidity and high final turbidity) have been applied to a study of normal individuals and individuals with coronary disease. The author is fully aware of the fallacy of considering any group of older individuals as "normal" with respect to atherogenesis, and for that reason it was decided to study both young and old "normal" individuals. As was noted above, both normal groups showed the same incidence of early development of turbidity, but there was a marked difference in mean final turbidity levels. This latter finding is probably a reflection of higher lipid levels in the older age groups. Simultaneous presence of both early turbidity and high final turbidity in the same serum was encountered in 64 per cent of the coronary group, 14 per cent of the older control group and 6 per cent of the young controls. It is apparent, therefore, that while either of the indices used permits some degree of discrimination between normal individuals and those with coronary atherosclerosis, the simultaneous presence of both indices is highly in favor of the presence of coronary atherosclerosis.

Eight out of 131 normal young individuals (equally divided as to sex) showed both early development of turbidity and high final turbidity. Six were males and four suffered from obesity. Thus both maleness and obesity were

TABLE 10.—*Summary of Serum Lipids in the Three Groups*

	Coronary Group		Old Controls			Young Controls		
	Mean	S.D.†	Mean	S.D.†	p*	Mean	S.D.†	p*
Free cholesterol mg.%	83.82	±22.61	65.96	±19.42	>.001	52.41	±16.40	>.001
Ester cholesterol	170.97	±54.75	164.83	±45.46	<.6	142.97	±37.98	<.001
Total cholesterol	257.69	±66.74	226.17	±52.18	<.01	195.88	±42.34	>.001
Lipid phosphorus mg.%	11.68	±2.63	10.40	±1.75	<.001	9.53	±1.70	>.001
Fatty acids of neutral fat mEq/L	5.67	±4.47	5.10	±3.57	>.6	3.44	±4.10	<.05
C/P molar ratio	1.79	±0.38	1.76	±0.35	<.6	1.77	±0.34	

* Probability of significant difference from coronary group.
† Standard deviation (σ) of mean.

disproportionately represented in the group which gave a positive test.

The data suggest that the "lecithinase test" may prove to be a useful clinical tool. Improvement in methods of standardization of enzyme and more accurate turbidity measurements may greatly enhance its value in individual cases. It is hoped that additional data will also be forthcoming on the nature of the lipoprotein changes.

SUMMARY

1. Alpha toxin of *Cl. welchii*, a potent lecithinase, disrupts the serum lipoproteins, releasing the lipids from their protein linkage, and causing intense turbidity in the serum. There is evidence to suggest that the enzyme may more specifically attack the less stable classes of lipoproteins.

2. The time taken for turbidity to occur, after enzyme and serum have been incubated under standard conditions, varies widely in the sera of different individuals. In this study it is shown that this phenomenon does not appear to depend on the rate of hydrolysis of lecithin, but is apparently dependent on other factors which govern lipoprotein stability. In 50 individuals with coronary disease, turbidity occurred early (less than 4.5 hours) in 72 per cent, while a similar phenomenon was seen in only 22 per cent of a control group of normal subjects of similar age, and in 21 per cent of a group of young normal individuals.

3. The degree of final turbidity correlates moderately well with the serum lipids as measured quantitatively. Final turbidity was higher in the coronary group (mean, 67.55) than in the older control (mean, 60.99) and young control groups (mean, 50.23).

Final turbidity estimation may be used as a screening technique for detecting individuals with abnormal serum lipid levels.

4. Early onset of turbidity, and high final turbidity reading were present simultaneously in 64 per cent of the coronary cases, 14 per cent of the older controls and 6 per cent of the young controls. The application of these criteria permits separation of individuals with coronary atherosclerosis from a control population.

5. The lecithinase test technic has been described, and the variability introduced by the enzyme and serum factors investigated. The test is not affected by storage of serum for periods of 7 to 10 days. Solutions of enzyme do not lose their potency for at least one month. Relatively stable values are obtained when individuals are retested for periods varying up to six months.

ACKNOWLEDGMENTS

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SUMARIO ESPAÑOL

1. La toxina alpha de *Cl. welchii*, una potente lecitinasa, desorganiza las lipoproteinas del suero, liberando los lípidos de su enlace con las proteinas y causando turbidez intensa en el suero. Hay evidencia que sugiere que la enzima puede mas especificamente atacar las lipoproteinas menos estables.

2. El tiempo tomado para la turbidez aparecer, luego de haberse incubado la enzima y el

uero bajo condiciones uniformes, varió grandemente en el suero de diferentes personas. En este estudio se demuestra que este fenómeno no aparece depender en la velocidad de la hidrolisis de la lecitina, pero es aparentemente dependiente en otros factores que gobiernan la estabilidad de la lipoproteina. En 50 individuos con enfermedad coronaria, la turbidez apareció bastante temprano (menos de 4.5 horas) en 72 por ciento, mientras que un fenómeno similar se vió en 22 por ciento de un grupo control de sujetos normales de similar edad y en 21 por ciento de un grupo normal de individuos jóvenes.

3. El grado de turbidez final correlaciona moderadamente bien con los lípidos del suero cuando se miden cuantitativamente. La turbidez final fué más alta en el grupo coronario (promedio 67.55) que en el grupo de controles viejos (promedio 60.99) y que en el grupo de controles jóvenes (promedio 50.23). La estimación de la turbidez final puede ser usada como una técnica encubridora para descubrir individuos con niveles anormales de lípidos del suero.

4. Aparición temprana de turbidez y turbidez alta final estuvieron presentes simultaneamente en 64 por ciento de los casos coronarios, 14 por ciento de los controles viejos y 6 por ciento de los controles jóvenes. La aplicación de estos criterios permite la separación de individuos con ateroesclerosis coronaria de la problación control.

5. La técnica de la prueba de lecitinasa se ha descrito y la variabilidad introducida por la enzima y los factores del suero se ha investigado. La prueba no es afectada al almacenar el suero por 7 o 10 días. Soluciones de la enzima no pierden su potencia por lo menos por un mes. Valores relativamente estables se obtienen cuando los individuos son probados una vez mas por períodos variando hasta seis meses.

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The Diffuse Vascular Lesion of So-Called "Thrombotic Thrombocytopenic Purpura"

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"Thrombotic thrombocytopenic purpura" is a thrombocytopenic, hemolytic disease with occlusive mounds in the arterioles and capillaries. These mounds have been popularly supposed to represent bland platelet thrombi. In recent years observations have been forthcoming in favor of a primary vascular lesion as the anatomic basis of the disease. This paper places special emphasis on the latter proposition, and pathologic material is presented to demonstrate how such a lesion probably evolves.

RECENT studies by pathologists, together with data from collateral sources, have made it apparent that the clinical disease now familiar to clinicians as "thrombotic thrombocytopenic purpura" is the result of primary damage to blood vessels, and should be included in the group of "diffuse vascular diseases."

First reported in the medical literature 27 years ago, its true character and morbid anatomy went long unappreciated by clinicians who confused it with idiopathic thrombocytopenic purpura, and by pathologists who interpreted the verrucal masses in dilated arterioles and capillaries as bland platelet thrombi. These misconceptions are currently in the process of being rectified. As a result antemortem diagnosis is feasible at the present time, and the primary degenerative change in the terminal blood vessels will soon be more generally appreciated.

HISTORICAL BACKGROUND

The obstacles to understanding this lesion were actually quite formidable. It was presented to medicine at a time when the concept of connective tissue ground substance as the site of biochemical and histologic abnormalities had not been widely adopted. Gerlach[29] was still developing his ideas on connective tissue injury in the Arthus phenomenon, and Klinge[44] had not published his monograph on rheumatic fever and the rheumatic diseases. In this country, though Libman and Sacks[46] had recently described the heart in disseminated lupus erythematosus, it was not until 1941 that the pathology of lupus was understood as a morbid process localized in the connective tissues.[42]

The original description of the disease is credited to Moschowitz in 1925.[50] His patient was a 16 year old girl with a two week course of weakness, pallor, fever, petechiae and profound anemia. No platelet count was recorded, but the hemoglobin was 40 per cent and the red blood cell count was 1,330,000 per cu.mm. The gross autopsy findings were not distinctive, but on microscopic examination Moschowitz saw what he interpreted as thrombi in the terminal arterioles and capillaries. The "thrombi" were surrounded by cells which he identified as fibroblasts. Fibroblastic penetration of the mass was noted with eventual formation of tuberclelike structures. Later observers have demurred from this interpretation of the cells seen capping the "thrombus." Impressed by the work of Flexner[24] with red blood cell toxins, Moschowitz concluded that the "thrombi" consisted of agglutinated and hyalinized erythrocyte masses and called the disease "an acute febrile pleiochromic anemia with hyaline thrombosis," caused by a powerful toxin with both agglutinative and hemolytic properties.

A different mechanism was proposed in

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1936 by Baehr, Klemperer and Schifrin.[6] They reported four cases in young and middle aged females with fulminant purpura hemorrhagica, thrombopenia, progressive anemia and prominent cerebral symptoms. They found innumerable hemorrhages in all serous and mucous membranes and within many viscera. Microscopically they observed thrombotic and proliferative lesions, most commonly in the arterioles and capillaries of the kidneys, heart, adrenals and pancreas. Proliferative changes in the lining endothelium of the involved vessels were seen, with actual invasion of the thrombotic mass, but they did not find evidence of organization. It was noted that in some areas the endothelial activity was out of proportion to the amount of thrombosis whereas in other situations the reverse was true. No parenchymatous changes were observed. The "thrombi" did not stain for iron or hemoglobin, and from the Giemsa stain it was concluded that they consisted of platelets. The thrombopenia was regarded as secondary to withdrawal of platelets into the occluding masses. Since the Giemsa stain cannot be considered specific for platelets the conclusions of these workers rested on very tenuous grounds.

In the same year Friedberg and Gross published a series of papers on nonbacterial thrombotic endocarditis associated with acute thrombocytopenic purpura,[25] and with prolonged fever, arthritis, inflammation of serous membranes and widespread vascular lesions.[26] One case in the former report was actually included in Baehr's protocols.[6] (Vide supra.) The latter paper[26] included at least one example of the disease under discussion. Case 2 of that group suffered from fever, profound anemia, and transient cerebral palsies, a combination later to be remarked upon many times in the clinical characterization of the disease. The "hyaline and granular plugs" in the heart, lungs, pancreas, thyroid and spleen leave little doubt about the identity of the lesions. Interestingly enough, Gross and Friedberg did not believe that the plugs were thrombotic. In ascribing them, on at least one occasion, to proliferation and desquamation of endothelium, they propounded the first definitely vasculogenic view of the lesion.[35]

The next communication pertaining to this entity was that of Gitlow and Goldmark in 1939.[30] Their effort was vitiated by the failure to clearly distinguish this disease from disseminated lupus erythematosus. Indeed, their second case was disseminated lupus with severe "wire loop" lesions in the glomeruli simulating thrombi.

During the following decade observations were made by a number of investigators, and by 1950 24 cases of the syndrome were available for analysis. Almost without exception endothelial proliferation was noted in and about the lesions and discussion concerned itself mainly with the significance of this finding. Thus Altschule[5] gingerly implied the presence of endothelial damage but pointed out that the origin of this damage was unknown. Conversely, Green and Rosenthal[33] and Bernheim[9] were unable to find endothelial aberrations where no "thrombi" were present, and the latter concluded that there was no morphologic evidence for endothelial disease. Trobaugh's[69] conclusions were essentially similar in that he regarded the process as being thrombotic. Fitzgerald in reporting three cases observed occasional independent endothelial changes but on the whole there were "overwhelmingly more thrombi," and referred to the disease as "thrombocytic acroangiothrombosis."[23] Employing differential stains for erythrocytes, hemoglobin, leukocytes, fibrin, bacteria and inclusion bodies, he decided, as Baehr and coworkers had done, that the masses were composed of platelets. Singer's conclusions were quite similar, and he contributed the popularly employed designation for the disease, "thrombotic thrombocytopenic purpura."[62]

However, observations critical of these formulations were not long in appearing. Muirhead[51] was impressed with the prominence of endothelial proliferation in his material, and Engel[20] noted swelling and proliferation of the capillary membrane. More significantly in Engel's slides, the blood vessel wall adjacent to the plugs showed degenerative changes and a few were frankly necrotic. This was especially prominent in the heart, kidneys and adrenals, though almost every

rgan was involved. At approximately the me time Carter[13] found conspicuous fibrinid degeneration in the arterioles of the heart nd kidneys, without any evidence of surounding inflammation. Plugged vessels were ost numerous in the heart, kidneys, adrenals, pleen and brain. There was, however, no odification of the "thrombotic" theory.

Evolution of Present Ideas

The work of Gore[32] represented a step away rom the simple "thrombotic" formulation. In studying five cases at the Army Institute of Pathology he found focal, "prethrombotic" lesions of the vessel wall. In essence it was described as a segmental accumulation of hyaline beneath the endothelium of a capillary and between the endothelium and media of an arteriole, usually the latter. The homogeneous substance tended to swell luminally, carrying before it an unaltered endothelium, and adventitially, producing a defect in the vessel wall. This swelling was thought to be due to imbibition of fluid from the circulation. When the process occurred rapidly the endothelium was broken, platelets accumulated over the defect, and the inaccessibility of antithrombic substances assured propagation of a thrombus which received a prompt endothelial investment. Lesions appeared to be in different stages, some showing organization and fibrosis, suggesting that the process had occurred in showers. Gore then clearly stated for the first time that the initiating factor was a focal vascular lesion.

At the same time Gore had accepted the conventional view that the verrucal portion of the lesion consisted of platelets. This point was examined critically in two papers by Meacham[47] and Orbison.[55] They stated unequivocally that "thrombotic thrombocytopenic purpura" is a collagen disease in which blood vessel damage is the primary event. They found characteristically an eosinophilic, smudgy (fibrinoid) mass replacing the normal fibrillar and cellular structure of the wall of involved arterioles and capillaries. The process was focal and segmental, and was seen occasionally without the intraluminal mound. When occlusions were present, these had the same tinctorial characteristics as the intramural fibrinoid material and appeared to be continuous with it. By camera lucida reproductions of serial sections Orbison[55] demonstrated a remarkable feature of the lesion in all organs, namely dilatation and cylindric aneurysm formation at the arteriolocapillary junction. Where the verruca joined the vessel wall, the elastica was destroyed and the media showed eosinophilic homogenization. It was concluded that such destruction and dilatation could not be caused by thrombi alone, and that the mural lesion was fundamental. However, an additive role by platelets in the formation of occlusive mounds could not be excluded. In discussing the difficulties pertaining to this matter, the above workers reiterate that platelets cannot be made to stain specifically. In their hands, the hematoxylin and eosin and periodic acid Schiff stains colored the mural and intraluminal material identically. Moreover when material from the lesions was compared with a suspension of platelets, and with the lesion of periarteritis nodosa tinctorially, they could not be distinguished, either by the periodic acid Schiff or Feulgen technics. Platelets, verrucal angionecrosis and amyloid stained metachromatically with toluidine blue, but there was no metachromasia with periarteritis material. Thus the reactions are parallel but not specific. Interestingly enough, though most studies of the subject continue to refer to "thrombotic thrombocytopenic purpura,"[7, 10, 14, 21, 27, 31, 39, 58, 66, 67, 70, 71, 74, 75, 76] a few of these include photomicrographs showing very clearly degenerative changes in the vessel wall underneath the "thrombus."[31, 39, 71]

In 1951, Allen referred to the disease under discussion as "arteriolocapillary thrombonecrosis." It was regarded as a "diffuse vascular disease," with fibrinoid degeneration of mural collagen and dilatation of terminal vessels as the primary event. Recently he has employed the term "thrombocytopenic verrucal angionecrosis"[2B] which he considers a more appropriate name. Allen considers that the verrucal lesion is almost exclusively a propagation of degenerated, swollen collagen, with only a negligible contribution of plasma, fibrin and

formed elements from the blood. This author likens the problem to that of degenerative verrucal endocardiosis (nonbacterial thrombotic endocarditis, terminal or marantic endocarditis),[3] also long regarded as a thrombotic valvular accretion of elements from the circulation. Systematic investigation with stains for collagen before and after tryptic digestion indicated very clearly that the verruca originated from degenerated valvular collagen and were aggrandized in only minor degree by plasma and cellular elements from the injured capillaries of the valve.[3]

The relevance of these investigations to "thrombocytopenic verrucal angionecrosis" is further underscored by the appearance in the latter disorder of atypical endocarditis.[6, 8, 20, 25, 27, 47] In one instance it appeared to be superimposed on a healed rheumatic valvulitis,[7] and in still another it was associated with *Staphyloccocus aureus* endocarditis.[11] Where detailed description of these vegetations is available,[6, 20, 25, 35] it is apparent that the verruca being described are the same as those appearing in degenerative endocardiosis. They are irregular, often large and friable, and have little or no tendency to extend on to the mural endocardium. Histologically they are a bland degeneration of collagen, lacking the granulomatous and vascular granulation elements of rheumatic fever, or the inflammatory-degenerative character of the Libman-Sacks endocarditis with its prominent cellular necrosis and hematoxylin body formation. And just as degenerative verrucal endocardiosis occurs in a variety of chronic infectious, degenerative, or neoplastic conditions, especially if rheumatic infection has deformed the valve, so verrucal angionecrosis may appear under very similar circumstances. Although limited mainly to the heart, in these circumstances, it is morphologically indistinguishable from lesions seen in clinically fulminating thrombopenia and anemia. Furthermore it has been described in the pathology of typhus fever.[4] Baehr and his colleagues[6] have also pointed out that inflammatory or thrombotic changes in a few vessels are frequently encountered in almost any type of infection, and Pagel[57] described similar plugs in the terminal vessels in subacute bacterial endocarditis. Indeed it would be of interest to study the incidence of thrombopenia and bleeding tendencies in a large group of patients who have long-term illnesses not directly involving the blood-forming organs, to determine whether these can be correlated with the appearance of verrucal lesions. Actually such a mechanism is not required to explain the thrombocytopenia here any more than it is necessary in idiopathic thrombocytopenic purpura where no lesions are found,[6, 23] or in disseminated lupus where one also frequently encounters thrombopenia and even sporadic verrucal angionecrosis.[34] For the recent work done on gamma globulin factors in lupus erythematosus,[37, 38] idiopathic thrombocytopenic purpura[23, 36, 65] and acquired hemolytic anemia,[15] indicate that abnormal immune globulins are responsible for diverse tissue and marrow alterations. Similar mechanisms may be operating in fulminating "thrombocytopenic verrucal angionecrosis" and in certain patients with chronic illnesses who develop endocardiosis and angionecrosis.

The relationship of this disease to disseminated lupus erythematosus has been suggested.[8, 30, 41] It is true that superficial similarities exist. Both occur in young women, and lupus may be associated with thrombopenia, hemolytic anemia or occluding vascular lesions, while verrucal angionecrosis may exhibit endocarditis, or, rarely, periarteriolar splenic fibrosis. At first blush this seems to make an impressive case, but the evidence does not remain convincing. The predominance of females over males is no longer as great in either disease as originally reported. The thrombopenia and hemolytic anemia are manifestations of disordered immune processes and cannot be given a more specific interpretation. The bland endocarditis in verrucal angionecrosis is quite different from the florid, alterative lesion of Libman-Sacks endocarditis, and in disseminated lupus the verrucal angionecrosis is inconstant, limited to the heart, and usually seen only when endocarditis is also present.[42] Finally periarteriolar fibrosis in the spleen has also been reported in three cases,[7, 8, 47] but in one case the angionecrosis

was limited to the heart and stigmata of lupus erythematosus were present,[8] and in a second case it was only suggestive.[47] Finally, though periarteriolar fibrosis is seen characteristically in lupus, it has been reported in other conditions and its specificity has been questioned.[68] Most writers now deny that the two diseases are related.[5, 6, 20, 32, 43, 62, 69]

Clinical Features

The diagnosis of "thrombocytopenic verrucal angionecrosis" is a challenge to the acumen of the clinician. Malaise, weakness, arthralgias, generalized body aches, headache and dizziness are fleeting prodromata. Antecedent upper respiratory infection is significantly frequent.[23, 62] Of the first 15 cases reported, 11 were females and four were males, but more recently the sex predilection has not been so striking.[7, 8, 16, 27, 47] Seventy-five per cent of the first 15 cases were less than 35 years of age, but in later reports the proportion of patients between 40 and 60 years has risen.[7, 8, 47] No race predilection has been established.

The prodromata soon give way to a hemorrhagic disease of explosive character, terminating in death within a few weeks of the onset. Ecchymoses and purpura appear on the skin, and epistaxis, hematuria and melena indicate diffuse bleeding from mucous membranes. These are usually present when the patient is first seen by the physician. In addition, pallor is striking and may even antedate the bleeding, further evidence of a hemolytic process.[62] Mild acholuric jaundice may accompany the pallor. The temperature is variable, low grade fever being present early in the disease, but a temperature of 106–107 F. terminally may be found, and indicates hemorrhage into the brain. The liver and spleen are palpable in about 50 per cent of the cases. Neurologic findings are of constant occurrence and figure predominantly throughout the course of the illness. The most common of these are headache, confusion, delirium, stupor, reflex changes, hyperesthesia, convulsions, facial weakness, hemiplegia, and coma. Occasionally neuropsychiatric symptoms initiate the illness. One patient was admitted in stupor and two in semicoma.[23, 67] In another case paranoid ideas were the presenting symptom,[7] and still another patient was admitted to a mental institution for depression.[31] An often mentioned characteristic of the mental and neurologic features is their remittent nature; the most alarming symptoms may regress in a matter of days, to be replaced by still others. This is in contrast to idiopathic thrombocytopenic purpura, where neurologic changes are less frequent, and when present, nonremitting. Excellent reviews of the neurologic aspects have been written.[1, 33]

Although in the majority of instances thrombocytopenic verrucal angionecrosis appears to arise *de novo* and run a fulminating course, occasional exceptions are noted. Meacham's case[47] lived for two years following splenectomy. In other instances[8, 11, 23, 27, 74] patients were ill for a number of years with cardiovascular, renal, arthritic or allergic diseases (urticaria, sulfa sensitivity), and the distinguishing features of verrucal angionecrosis occurred only terminally, or at autopsy. In two patients the verrucal lesions were limited to the heart and skin, respectively.[8] A case has been seen by the present author in which the lesions were limited to the kidney and heart. Amyloidosis of the secondary type was present. The patient was a 31 year old male patient who had been ill for seven years before death with intermittent migratory arthralgia, mitral murmurs and a fever of unknown origin. He had multiple admissions and finally died in heart failure with enlarged heart, pericardial friction rub, arthralgias, hemolytic anemia, purpura, and epistaxis. No platelet count was done. These experiences suggest that the lesion may occur in marked form as a terminal phenomenon and as a sequel to an antecedent disease, especially one of the collagen group. The patient cited above was thought to have rheumatic fever and rheumatoid arthritis.

Laboratory Profile

The most constant laboratory findings are thrombocytopenia and hemolytic anemia. The anemia is usually normochromic with the hemoglobin dropping to 3 to 5 Gm. per 100 cc.,

and the red blood cells to 2.5 million per cu.mm. or lower. There is commonly a leukocytosis of 12 to 15,000 per cu.mm., and the differential count is shifted to the left. Nucleated red blood cells, reticulocytosis, inconstant spherocytosis and terminal leukemoid reactions are not uncommon. The platelet count may be only moderately depressed early in the disease, but counts of 30,000 per cu.mm. or less are the rule when the syndrome is well developed.

The hypotonic saline fragility is usually normal, but may be increased when spherocytosis appears.[47, 51, 63] Singer found the acid (heat) fragility normal, but the mechanical fragility was definitely increased, suggesting the pattern of acquired hemolytic anemia to that investigator.[63] The Coombs test was negative in his patient and others have had the same experience.[7, 27, 47, 75] The bleeding time is regularly increased and the tourniquet test is positive.

The bone marrow is usually hyperplastic and the megakaryocytes are normal or increased. Although Singer found normal platelet maturation,[63] deficient or absent thrombocyte production was noted by Meacham,[47] Barondess,[7] Cooper,[16] and Green,[75] a situation similar to that found in idiopathic thrombocytopenic purpura.[18] Cooper[16] has found the pathognomonic vessel lesion in the marrow by examining paraffin sections of sternal aspiration material.

The serum bilirubin is usually elevated to 2.5 to 4.0 mg. per 100 cc. with the indirect reaction predominating. Fecal and urinary urobilinogen are increased, but Singer considers the acholuric jaundice to be a more constant indication of hemolysis.[63] The total proteins and serum globulin may be elevated, but this is not a consistent finding. The "L.E." cell test has been reported negative,[7, 16, 27, 75] but biologic false positives for syphilis are seen.[11, 16, 27]

The antemortem diagnosis of thrombocytopenic verrucal angionecrosis was first made by Engel in 1947,[20] then by Singer in 1950.[63] Meacham made it from splenectomy material in 1951.[47] The disease simulates many of the hemorrhagic disorders and the diagnosis can be established only by close attention to clinical detail. The combination of acquired hemolytic anemia and thrombocytopenic purpura not readily explained by a history of toxins, drug idiosyncrasy or bone marrow invasion (tumors, lymphoma, leukemia, lipoid histiocytosis, granulomata) should awaken suspicion. Idiopathic thrombocytopenic purpura is not usually associated with hemolytic anemia and the spleen is invariably not palpable. Fluctuating, transient neurologic signs are very characteristic of verrucal angionecrosis, and not at all frequent in idiopathic purpura in which central nervous system involvement, when it occurs, is usually in the form of severe hemorrhage. Finally the identification of the involved vessels in paraffin sections of marrow aspirates, as reported by Cooper, offers a promising approach.[16] Meacham has suggested that the lesions might be found in skin biopsies.[47]

Prognosis and Treatment

This disease is uniformly fatal. One patient of Meacham's survived 2.5 years following splenectomy,[47] but in every other instance the results of this procedure have been discouraging.[6, 7, 20, 33, 51] Likewise corticotropin (ACTH)[7, 27, 47, 75] and cortisone[16] have had no truly beneficial effects.

Histogenesis

The histogenesis of verrucal angionecrosis is well demonstrated in the following case report.

The patient was a 29 year old male Italian leather worker admitted with a characteristic history of headache, bleeding gums, and sore throat for three days, and hematuria of 24 to 48 hours duration. He had pallor, purpura of the lower extremities and spongy, friable gums. The liver and spleen were not palpable.

Admitting laboratory data were as follows: Red blood cells 2.5 million per cu.mm., hemoglobin 8.0 Gm. per 100 cc., platelets 225,000 per cu.mm., white blood cells 12,000 per cu.mm., hematocrit 23 per cent. Examination of the urine showed 2 plus albumin, many white blood cells and red blood cells and occasional granular casts. The blood chemical findings were: urea nitrogen 21.6 mg. per 100 cc., total protein 7.2 Gm. per 100 cc., albumin 4.5 Gm. per 100 cc., globulin 2.7 Gm. per 100 cc., cholesterol 116 mg. per 100 cc., esters 78 mg. per

100 cc., cephalin flocculation test negative and alkaline phosphatase 3.4 mg. per 100 cc.

The patient ran a febrile course, 105F., and rapidly deteriorated. There was continued hematuria and hemorrhage into the skin. The hemoglobin dropped to 3.6 Gm. per 100 cc., and the red blood cells to 1,300,000 per cu.mm. Icterus was present and the urine was positive for hemoglobin. On the tenth hospital day he developed right facial weakness and paralysis of the right arm. He died on the fourteenth hospital day in coma. The final hemoglobin was 3.6 Gm. per 100 cc., the platelet count was 14,650 per cu.mm., and the icterus index was 45.

At autopsy there were subconjunctival ecchymoses and purpura of the extremities. Hepatosplenomegaly was present. Petechiae and purpuric spots were found throughout the viscera, especially the heart and kidney. There was leptomeningeal hemorrhage over the left frontal pole and in the central white matter of the left frontal lobe. Smaller hemorrhages were found in the right hippocampal gyrus, in the marginal cortex of the right central and calcarine fissures, and on the left lateral aspect of the corpus callosum. They varied from a few millimeters to one centimeter in size. A few millimeter-sized hemorrhages were also seen in the right cerebellar peduncle.

Figure 1 is a photomicrograph of the kidney, showing a distal interlobular vessel in two sections. The section of vessel further from the glomerulus shows focal eosinophilic necrosis in its wall. This

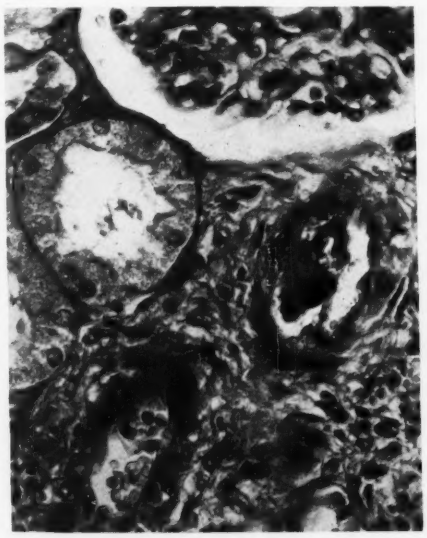

FIG. 1. Kidney. H & E stain. ×440. Two segments of a distal interlobular vessel showing earliest and more advanced stages in the development of the lesion. The section nearer the glomerulus shows verruca formation. (For details see text.)

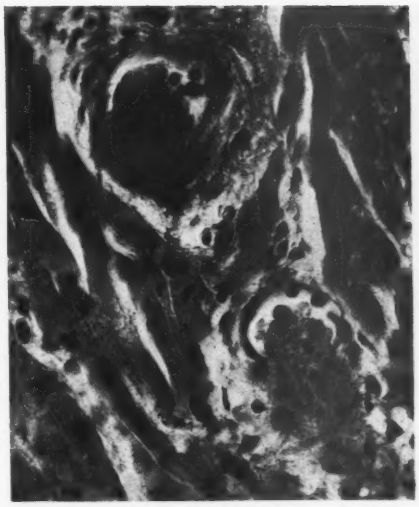

FIG. 2. Heart. H & E stain. ×440. A verrucal lesion in an intramyocardial capillary. Note slit-like, eccentric lumen. (For details see text.)

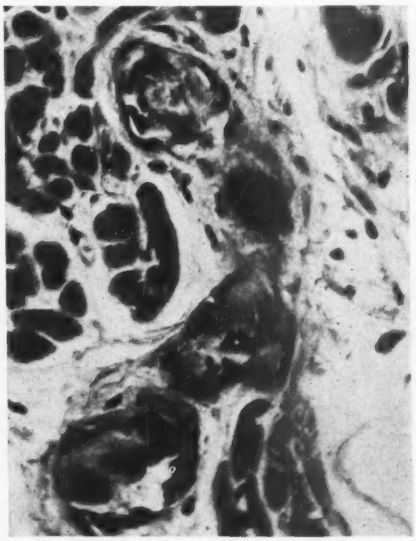

FIG. 3. Heart, arteriole. Elastic stain. ×440. The elastic stain shows fraying and destruction of elastica in the vicinity of the lesion.

represents the earliest change. Note that at this point the wall of the vessel is slightly thickened. The intima is destroyed and the amorphous eosinophilic material bulges slightly into the lumen. Likewise the outer border of the vessel at the point of change is ragged and indefinite. The adventitia

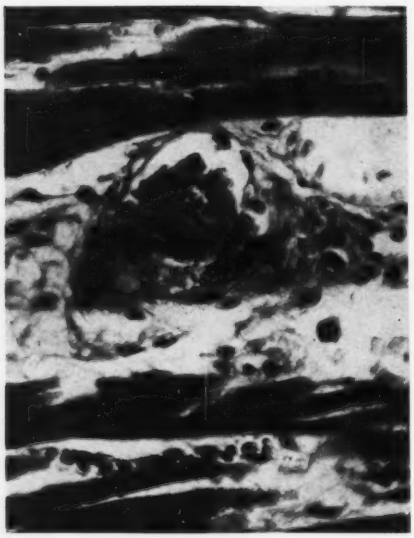

FIG. 4. Heart. H & E stain. ×440. As in figures 1 and 2 there is destruction of the vessel wall at the site of verruca formation.

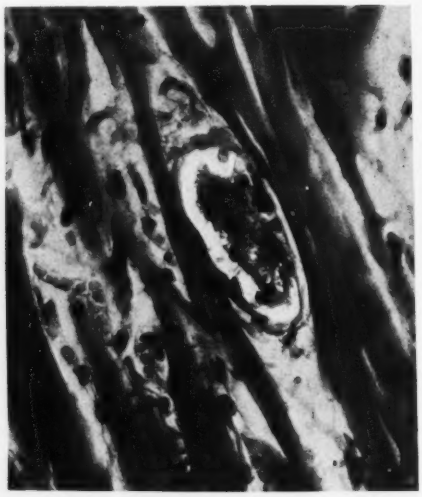

FIG. 5. Heart. H & E stain. ×440. Note bland "thrombus" in greatly dilated capillary. (For details see text.)

is not identified as a smooth line, and the eosinophilic material appears to merge imperceptibly with the perivascular tissue. The section nearer the glomerulus shows the lesion in a much advanced stage. The necrotic material has extruded itself into the lumen, forming a verrucal mass capped with hyperplastic endothelial cells which have plump vesicular nuclei. There is no inflammatory reaction or scarring. Figure 2 shows the verrucal lesion in capillaries of the heart. The intramural degeneration has greatly thickened the wall and bulged into the lumen, converting it into an eccentric slit. Note the continuity between the intraluminal material and the altered vessel wall. The capillary is also greatly dilated. Aneurysmal dilatation is an integral part of the process in consequence of connective tissue and elastic destruction. Figure 3 is an elastic stain of myocardium, showing the fraying and destruction of the elastica in the vicinity of the lesion. In figure 4 the neurogenic origin of the degenerated luminal mound is again demonstrated. Although the verruca originates at the site of vessel injury, it soon propagates down the lumen. This growth is due to further intramural connective tissue degeneration, to transudation of fluid from the blood, and probably to some accretion of fibrin and formed elements. This propagated portion of the "thrombus" is also rapidly endothelialized, forming a sleeve. Fortuitous sections through this portion show what appears to be a bland thrombus with no attachment to the vessel wall. Figure 5 shows such a bland "thrombus," in a dilated capillary, and with an endothelial investment. Although almost every vessel was involved in this case, there is no necrosis, fibrosis or infiltration of the myocardium or other organs (fig. 6).

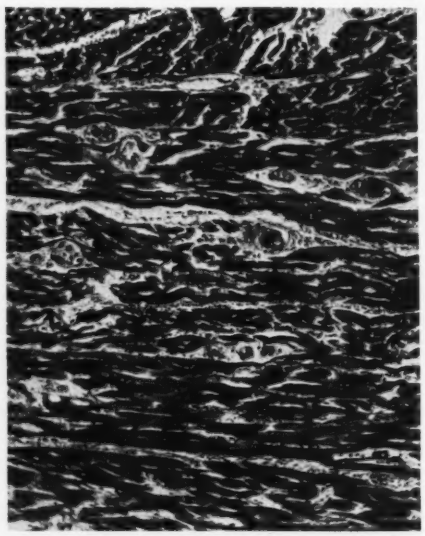

FIG. 6. Heart. H & E stain. ×100. Many lesions are present. Note absence of necrosis, fibrosis, or cellular infiltration.

Etiology and Pathogenesis

The etiology and pathogenesis of "thrombocytopenic verrucal angionecrosis" presents the same elusive complexities as those pertaining to the collagen diseases in general. In these disorders hypersensitivity may be suggestive or explicit, but the nature of the antigen has often evaded scrutiny, and the mechanism by which an antigen causes observable histopathologic changes remains obscure. In periarteritis due to sulfa,[48] penicillin,[72] horse serum,[59] or iodine,[60] for example, the nature of the antigen is apparent, as it also is with rheumatic fever which can be reproduced experimentally with heterologous streptococci[53, 54]; so too with glomerulonephritis, which is producible with streptococci and serum[49] or bovine globulin.[73] In disseminated lupus erythematosus, on the other hand, the allergen is not apparent, but other considerations such as the antigenic nature of the L.E. cell[38] make it permissible to classify it as a hypersensitivity disease, at least tentatively. "Thrombocytopenic verrucal angionecrosis" appears to occupy an intermediate position in this respect. Interestingly enough, siblings of patients with the disease have had idiopathic thrombocytopenic purpura,[6] or died of disseminated lupus,[63] or periarteritis nodosa.[9] Two verrucal angionecrosis patients are known to have had antecedent rheumatic fever.[7, 23]

Since this disorder is not a "thrombosis," hypotheses relating to abnormalities of the blood clotting mechanism,[9, 13] or to endothelial toxins[30] are not applicable. The Schwartzmann phenomenon[28, 61] as a possible prototype of the lesion has been adequately controverted by Gore.[32]

The almost constant occurrence of upper respiratory infection and pharyngitis shortly before the acute stage of the disease is striking.[6, 16, 20, 23, 30, 62, 69] This is significant not from the point of view of viral or bacterial etiology, but because of possible hypersensitivity factors that infection might incite. For patients with this disease often exhibit allergies and drug idiosyncrasies, and at times these might even be regarded as causative. Urticaria[6, 23] and adhesive tape dermatitis[9] have been noted and in three patients small pox vaccine,[33] tetanus antitoxin[7] and milk protein[67] were administered shortly before the onset of the illness, and cannot be excluded as contributory factors. More constant and convincing is the sensitivity exhibited to sulfa,[8, 11, 20, 23, 62, 70] penicillin,[27, 70] and iodine.[19] Usually the sulfa or penicillin were taken for an infection (respiratory, pharyngitis, arthritis, adenitis or genitourinary infection). The evidence of drug reaction such as chills, fever, malaise, arthralgias, diffuse skeletal pain and hematuria often directly anteceded the onset of the fatal disease. Ehrich's patient took a reducing drug containing 0.3 mg. of elemental iodine in each tablet.[19] At autopsy the iodine was recovered from the tissues by chemical assay. Muirhead[51] and Gore[32] have reported glomerulonephritis in their cases, and this finding along with the thrombopenia and hemolytic anemia which are invariable features of the disorder may be interpreted as a manifestation of hypersensitivity. For though Bernheim[9] could not demonstrate an antiplatelet factor in the postmortem blood of one patient and though the Coombs test was negative in the few instances when it has been done,[7, 27, 47, 63] too little attention has been given to the immunologic aspects of verrucal angionecrosis. Now that the diagnosis can be made ante mortem, opportunities will present themselves for further study, and it is likely that "factors" will be found just as they have been in idiopathic thrombocytopenic purpura[22, 36, 65] and acquired hemolytic anemia.[15]

Finally though allergic evidence is impressive it is well to be circumspect in excluding other possible agents. For just as fibrinoid degeneration can be induced in blood vessels by nonantigenic methods,[52, 56] and periarteritis nodosa has been noted in rats in the presence of rapidly rising blood pressure,[17, 64] so the lesion of verrucal angionecrosis is seen in photomicrographs of vessels from dogs made hypertensive and azotemic by bilateral nephrectomy[45, 52, 56] or other procedures resulting in hypertension.[12] It is apparent then, that intravascular stress, azotemia, hormones,

pressor substances or other factors may produce the lesion of verrucal angionecrosis as well as those of periarteritis and malignant arteriolosclerosis, and any truly valid pathogenetic concept must integrate all of these variables.

Summary

1. The purpose of this paper has been to support the thesis that so-called "thrombotic thrombocytopenic purpura" results from primary damage to arterioles and capillaries, and is therefore a "diffuse vascular disease."

2. The evolution of the literature on the subject has been traced, and a review of the clinical, laboratory and therapeutic aspects of the disease has been offered. As regards the historical development of the subject, special emphasis has been placed on the observations of Orbison, Meacham, and Allen, which suggest that primary damage to the terminal portions of the vascular system in many organs is the essential pathologic process.

3. A case which has come under the author's observation is presented in detail. From this material representative sections are employed to illustrate the histogenesis of the lesion from the early stage of intramural vascular necrosis to the fully developed and propagated "bland thrombus."

4. Although no abnormal globulin "factor" has been isolated in this disease certain clinical and hematologic characteristics suggest that it is related to diseases like acquired hemolytic anemia, thrombocytopenic purpura, and disseminated lupus erythematosus, in which abnormal immunologic mechanisms have been demonstrated.

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Sumario Español

1. El propósito de este trabajo ha sido sostener la tesis de que la "púrpura trombótica trombocitopénica" resulta del daño primario a las arteriolas y capilares y por lo tanto es una "enfermedad difusa vascular".

2. La evolución de la literatura sobre este tema ha sido trazada y un repaso de los aspectos clínicos, de laboratorio y de terapéutica de la enfermedad se ofrece. En cuanto concierne al desarrollo histórico del tema, se le ha dado especial énfasis a las observaciones de Orbison, Meacham y Allen, que sugieren que el daño principal a las porciones terminales del sistema vascular en muchos órganos es el proceso patológico esencial.

3. Un caso observado por el autor se discute en detalle. De este material secciones representativas se emplean para ilustrar la histogenesis de la lesión del primer estado de necrosis intramural vascular al "trombo blando" completamente desarrollado y propagado.

4. Aunque ningún "factor" de globulina anormal ha sido aislado en la enfermedad algunas de las características clínicas y hematológicas sugieren que esta relacionada a enfermedades como la anemia hemolítica adquirida, púrpura trombocitopénica y el lupus eritematoso diseminado, en las cuales se han demostrado mecanismos anormales inmunológicos.

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Therapy of Gram Positive Bacteremias With Presentation of Four Cases

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Improvement of therapeutic results in bacteremias due to the "resistant" organisms, staphylococci and enterococci, can best be achieved by a critical analysis of current concepts and adherence to certain fundamental principals. Experience with four successfully treated cases of this group of gram positive bacteremias is presented and specific therapeutic recommendations are set forth.

THE BACTEREMIAS, despite more than a decade of experience with active therapeutic agents, remain a complicated and difficult problem. The results obtained during the sulfonamide era, with only 5 to 10 per cent cures, were disappointing.[1] With the advent of penicillin the average cure rate of bacteremia rose to 70 per cent, where it has remained despite an increasing number of available antibiotics.[2] During recent years a significant, and probably growing proportion of penicillin-resistant cases has been encountered. This aspect of the problem is largely attributable to the increased incidence of cases infected with enterococci and penicillin-resistant staphylococci. Dowling and coworkers[3] have recently estimated that 300 new cases of staphylococcic endocarditis develop in the United States each year. Concurrently the ratio of *Streptococcus viridans* to staphylococcus endocarditis has been reported as 2.6 to 1,[3] compared with the ratio of 7.4 to 1 reported by Thayer in 1926.[4] In addition to this increasing incidence, both enterococcic and staphylococcic organisms have been shown to be more resistant to therapy than *Streptococcus viridans*. Widespread use of the newer antibiotics, such as chlortetracycline, oxytetracycline and chloramphenicol has not only failed to improve the situation, but has resulted in a high percentage of relapses and therapeutic failures.[5] This failure of the broad spectrum antibiotics is primarily due to the fact that these agents, like the sulfonamides, are mainly bacteriostatic rather than bactericidal. Evolving from these considerations it might be postulated that an arbitrary line is being drawn between the bacteremias which can be cured with relative ease and those where treatment failures are common. Those due to *Streptococcus viridans* belong to the first group, while infections due to the staphylococci and enterococci constitute the most important members of the second group.

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Case Reports

The following case reports constitute all cases of gram positive bacteremias treated on the Medical Service of this hospital over a two year period from August 1951 to August 1953.

Case 1. The patient, a 28 year old, white, male Sergeant, was initially hospitalized on Aug. 11, 1951, with a chief complaint of right lower quadrant pain. The significant findings on physical examination were an apical systolic murmur transmitted into the aortic area, moderate hepatomegaly, and clubbing of the fingers. Because of temperature elevation of 101 to 102 F., blood cultures were obtained. These cultures were positive for nonhemolytic streptococcus, subsequently identified as *Streptococcus liquefaciens*. By August 1951, the patient was noted to have splenomegaly and was manifesting embolic phenomena. Therapy was initiated on Aug. 25, 1951, consisting of streptomycin, 3 Gm. intramuscularly, daily, penicillin, 10,000,000 units daily by continuous intravenous drip, and sulfadiazine, 1 Gm. orally every four hours. This form of therapy was terminated on Aug. 31, 1951, in favor of chlortetracycline, 2 Gm. daily by the oral route, as the result of sensitivity studies by the disc method which revealed the organism to be sensitive to chlortetracycline, chloramphenicol, oxytetracycline, moderately sensitive to streptomycin, and resistant to penicillin. After two weeks of chlortetracycline therapy the patient had become afebrile and no longer manifested emboli-

phenomena. The drug was continued for an additional two weeks, following which daily blood cultures were obtained. The patient was well until Oct. 15, 1951, when fever and embolic phenomena recurred. Blood cultures were again positive for *Streptococcus liquefaciens*, and antibiotic therapy was resumed, consisting of 25,000,000 units of penicillin and 2 Gm. of streptomycin daily. Sensitivity studies were again carried out, utilizing the disc method, and the organism reported as sensitive to 10 units per cubic centimeter of penicillin, and moderately sensitive to streptomycin. By Nov. 1, 1951, the patient's disease again manifested itself by fever and embolic phenomena, and the patient was transferred to Fitzsimons Army Hospital. On admission the positive physical findings included a systolic murmur over the entire precordium, splenomegaly, and generalized lymphadenopathy. The patient was placed on an antibiotic regimen consisting of chlortetracycline, 2 Gm. daily, and oxytetracycline, 4 Gm. daily, orally. This was continued until Dec. 23, 1951, during which time the patient's temperature became normal. He remained afebrile until Jan. 8, 1952, when the fever recurred and blood cultures were again positive for *Streptococcus liquefaciens*. On this occasion the freshly isolated organism was reported as sensitive to 8 units of penicillin per cubic centimeter and resistant to all other antibiotics by the disc method. Therapy was resumed on Jan. 12, 1952, consisting of 25,000,000 units of penicillin by continuous intravenous drip, 2 Gm. of streptomycin, intramuscularly, and 2 Gm. of probenecid, daily. On Jan. 22, 1952, penicillin dosage was increased to 40,000,000 units daily, and this combination was continued until March 9, 1952, when it was terminated. Bioassays revealed serum penicillin levels ranging from 50 to 75 units per cubic centimeter. The patient remained completely afebrile after Jan. 28, 1952, the last positive blood culture having been obtained on Jan. 11, 1952. He was followed for a period of two months after termination of antibiotic therapy and remained completely asymptomatic and afebrile during this period.

Comment. Two of the three relapses in this case demonstrate the fallacy inherent in the administration of bacteriostatic rather than bactericidal agents. The third relapse may be attributed to inadequate dosage of bactericidal agents resulting in failure to obtain bactericidal effect. Two highly significant defects thus become apparent in the disc method of estimating antibiotic sensitivity: (1) Only inhibition of organism growth is revealed. (2) It is impossible to relate zones of inhibition to the milliliter concentration of drug required. Although it is possible to subculture from the inhibition zone to determine whether viable organisms are present, this is an unreliable and impractical method for which the tube dilution-plate method is to be preferred. This method is performed in the following manner: a drop of 18 hour broth culture inoculum with a density equivalent to a number 3 nephelometer tube (900,000,000 organisms per milliliter) is added to appropriate concentrations of the antibiotic diluted in tryptose phosphate broth. This may be set up as a series of two-fold dilutions of the antibiotic through the desired range of concentrations to be evaluated. Tubes are incubated at 37 C. overnight and all turbic tubes are read as manifesting resistance to the respective concentration of the drug. Nonturbid tubes are reincubated for an additional period to permit revitalizing the antibiotic sensitized organism. At the 24-hour level readings are made to determine if complete resistance was evidenced as previously manifested by turbidity. Lack of turbidity is not accepted as anything more than inhibition. At 48 hours all clear translucent tubes are plated to blood agar and any growth is considered as evidence of bacteriostasis, while the absence of growth is considered as evidence of complete inhibition, or, for practical purposes, bactericidal effect. The testing of a combination of antibiotics is performed in essentially the same manner.

Case 2. The patient, a 28 year old white woman, entered Fitzsimons Army Hospital for the second time on Nov. 20, 1952, for re-evaluation of a patent ductus arteriosus complicated by staphylococcus bacteremia. She was initially admitted to Fitzsimons Army Hospital in August 1952, for surgical treatment of a patent ductus arteriosus, which was ligated. The immediate postoperative course was uneventful. However, on the sixth postoperative day the patient was found to have a loud pulmonary systolic murmur, grade III–IV in intensity, accompanied by a systolic thrill. At that time it was considered that the ductus had been incompletely obliterated at surgery. The patient was subsequently discharged to return in two months for re-examination and re-evaluation. Three weeks following discharge the patient developed sudden onset of chills and fever and was hospitalized elsewhere. Blood cultures were found to be positive for *Micrococcus pyogenes var aureus*. In vitro bacterial antibiotic sensitivity studies revealed the organism to be resistant to penicillin, bacitracin, streptomycin, chlor-

amphenicol and moderately sensitive to chlortetracycline and oxytetracycline. The patient was therefore treated with three courses of oxytetracycline, given orally in the amount of 4 to 6 Gm. daily. She initially appeared to respond to the oxytetracycline, but symptoms recurred when the drug was discontinued. On Nov. 20, 1952, the patient was readmitted to Fitzsimons Army Hospital. On this admission she was feeling well and was afebrile, but had the classic findings of a patent ductus arteriosus and a palpably enlarged spleen. No therapy was initiated on this admission. By Nov. 23, 1952, the patient was acutely ill with chills and fever, and blood cultures were positive for *Micrococcus pyogenes var aureus*, which was found to be resistant to all concentrations of penicillin ranging from 1.5 units per cubic centimeter to 100 units per cubic centimeter by the tube dilution-plate method. On Nov. 23, 1952, prior to the reporting of the above sensitivity studies, the patient was started on penicillin, 25,000,000 units daily by continuous intravenous drip, combined with streptomycin, 2 Gm. intramuscularly daily, and probenecid, 2 Gm. orally in divided doses daily. By Nov. 25, 1952, the patient had shown no improvement so the daily dosage of penicillin was increased to 50,000,000 units. On the following day the patient's condition appeared even worse and the penicillin dosage was increased to 100,000,000 units daily by continuous intravenous drip. By the afternoon of Nov. 28, 1952, it was apparent that this antibiotic therapy was ineffective and the patient would have to be operated upon in spite of her critical condition in the hope of obtaining a surgical cure. Penicillin and streptomycin were discontinued and the patient was placed on oxytetracycline, 2 Gm. daily, in the hope that this would lower her temperature and improve her general condition.

She was re-operated on Dec. 1, 1952, at which time an abscess was found in the upper mediastinum, which was incised and drained of pus positive for *Micrococcus pyogenes var aureus*. The mediastinal abscess connected directly with the patent ductus. No attempt was made to divide the ductus in view of the septic field, but it was ligated with several chromic sutures. The patient tolerated the surgical procedure fairly well, but continued to be acutely ill. Further bacterial sensitivity studies revealed that a combination of oxytetracycline, erythromycin, and bacitracin were bactericidal in the amount of 8 micrograms of oxytetracycline, 1.6 micrograms of erythromycin and 8 micrograms of bacitracin combined. On Dec. 4, 1952, the patient was placed on erythromycin, 0.5 Gm. every six hours and bacitracin, 10,000 units every four hours intramuscularly, in addition to the oxytetracycline, 2 Gm. intravenously daily. On December 5, the patient showed evidence of congestive heart failure and was therefore digitalized. After one week of the above antibiotic therapy the oxytetracycline was reduced to 1 Gm. intravenously daily. By December 18 the patient refused more intravenous therapy. At that time her temperature was falling but had not returned to normal. Consequently oxytetracycline was changed to the oral route, the patient receiving 1 Gm. every four hours. A few days later her temperature returned to normal. By December 27 the urinary sediment revealed abnormal findings so the bacitracin was discontinued, the oxytetracycline and erythromycin being maintained. On Jan. 1, 1953, the patient relapsed with chills and fever. Blood cultures were again positive. On that date oxytetracycline and erythromycin were discontinued and she was placed on neomycin, 0.5 Gm. intramuscularly every 12 hours, which had been shown to be bactericidal at a level of 0.5 micrograms per cubic centimeter in vitro by the tube dilution-plate method. This therapy was continued until January 21 when it was terminated because of nephrotoxicity manifested by abnormal urinary sediment.

No therapy was administered after January 21 and the patient remained afebrile; she felt well, and blood cultures were negative. She manifested gradual clearing of the moderately abnormal urinary sediment. However, urinary function studies continued to show inability to concentrate the urine above 1.010 after 24 hours of dehydration. On March 12, 1953, a follow-up evaluation was performed, at which time blood cultures were found to be negative and the blood urea nitrogen normal. However, she was still unable to concentrate urine above a specific gravity of 1.010. On August 29, 1953, the patient returned for further follow-up evaluation, at which time she complained of loss of hearing, which had been progressive since first noted one month following the termination of neomycin. Otologic evaluation revealed a primary acoustic neuritis with inner ear deafness, bilateral and severe, which the consultant considered to be permanent but not progressive. The remainder of the examination revealed the patient to be in excellent general condition, tolerating full activity without restriction. The previous impairment of renal function had returned to normal.

Comment. This case presented the problem of a subacute bacterial endarteritis due to *Micrococcus pyogenes var aureus*, which manifested resistance to the common forms of therapy. Therapy was delayed until after positive blood cultures had been obtained and the organism identified. Because of her precarious condition it was necessary to begin the most logical form of treatment before the in vitro sensitivity studies were completed. As it became apparent that the bacteremia was not controlled, the penicillin dosage was elevated rapidly to 100,000,000 units daily

along with 2 Gm. of streptomycin and 2 Gm. probenecid. As a result of continued deterioration in the patient's condition, it soon became evident that this antibiotic regimen would not suffice. Completion of the antibiotic sensitivity studies revealed that the organism was resistant to penicillin in concentrations ranging from 1.5 Oxford units per cubic centimeter to 100 Oxford units per cubic centimeter, but sensitive to 100 micrograms of dihydrostreptomycin. Several in vitro combinations were tried with the following results:

Bactericidal effect with combination of...	10 mcg. oxytetracycline 2 mcg. erythromycin
Bactericidal effect with combination of...	16 Oxford units penicillin 8 mcg. oxytetracycline 8 mcg. bacitracin
Bactericidal effect with combination of...	8 mcg. oxytetracycline 8 mcg. bacitracin 1.6 mcg. erythromycin

It was hoped that surgical intervention might result in a cure, and immediately following surgery the oxytetracycline, erythromycin, bacitracin combination, which appeared to be most efficacious in vitro, was instituted. Subsequently the bacitracin was stopped because of the signs of nephrotoxicity. After the patient refused further intravenous therapy it became impossible to maintain an adequate blood level of oxytetracycline because the oral preparation caused nausea and vomiting to the point of inanition. At this point in vitro sensitivity studies were carried out with neomycin revealing the organism to be sensitive to a concentration of 0.5 micrograms per cubic centimeter. Since the patient had recovered from the previous nephrotoxic effect of bacitracin, and with close check for signs of toxicity, Neomycin was instituted and continued for a period of 21 days, at which time evidence of nephrotoxicity was again manifest and all drug therapy was discontinued, with the hope that an adequate period of clinical and laboratory "cure" had been effected. It seemed justifiable to state that without (1) adequate bacteriologic studies, (2) surgical drainage of the mediastinal abscess, and (3) the discovery of the efficacy of newer antibiotics, both singularly and in combination, this case would have terminated fatally. Neomycin contains both nephrotoxic and ototoxic factors which appear to be due partly to impurities and partly to the active drug itself. Although the drug was discontinued in this case because of the appearance of nephrotoxicity, the most prominent toxic effect subsequently proved to be the ototoxicity. This patient received 20 mg. per kilogram of neomycin daily for a period of 21 days, thus confirming the experience of others[6] that doses in the range of 15 to 20 mg. per kilogram cannot be administered for relatively long periods of time without adverse effects.

Case 3. The patient, a 36 year old woman, was admitted to Fitzsimons Army Hospital on Dec. 19, 1952, with chief complaint of fatigue, fever, and painful nodules in the skin of the right foot and left chest, of six weeks duration. There was no past history of acute rheumatic fever, although she had scarlet fever at the age of 8 years, and was known to have had a heart murmur since the age of 12 years. In August 1952, the patient experienced an episode of right costovertebral angle pain attended by fever and genito-urinary symptoms. She was treated with chlortetracycline by a local physician and had a complete genitourinary workup, including cystoscopy. Two weeks later the patient noted the onset of what she described as "flu," characterized by low-grade fever, generalized muscular aches, headaches, lethargy and weakness. From the time of onset of this illness until Dec. 9, 1952, the patient was treated intermittently with chlortetracycline by her local physician. She had at least five exacerbations of her symptoms, all of which responded to chlortetracycline, but with recurrence of symptoms following termination of this form of therapy. Physical examination at the time of admission revealed the presence of embolic nodules in the skin of the left chest and the lateral aspect of the right foot. There were no other skin lesions or further evidence of petechiae. Examination of the heart revealed a rough systolic murmur heard in the mitral area, grade III in intensity, radiating toward the axilla and left sternal border. A palpable spleen was present.

Blood cultures were obtained and were positive for *Streptococcus faecalis*, subsequently shown on the basis of gelatin liquefaction to be *Streptococcus liquefaciens*. This same organism was likewise cultured from the urine on several occasions during the first week of hospitalization. Sensitivity studies were performed and a bactericidal effect was found in vitro with 25 micrograms of streptomycin, and 100 units of penicillin per cubic centimeter in com-

bination. The organism was also demonstrated to be sensitive to 15 units of bacitracin, but resistant to all other antibiotics, both alone and in combination. On Dec. 27, 1952, she was started on crystalline penicillin, 50,000,000 units daily by continuous intravenous drip, streptomycin, 2 Gm. intramuscularly daily, and oral probenecid, 2 Gm. daily. Weekly blood cultures were obtained throughout the hospital course but remained negative subsequent to the fifth day following admission. Serum antibiotic assays were performed periodically revealing a combined antibiotic activity equal to 150 Oxford units of penicillin and streptomycin, with penicillin activity equalling 125 units per cubic centimeter and streptomycin activity equalling 25 micrograms per cubic centimeter. The patient did well on therapy and remained afebrile throughout the remainder of her hospitalization. By Feb. 6, 1953, the patient had completed six weeks of antibiotic therapy and she complained considerably of dizziness, which was attributed to the streptomycin therapy. Prior to discharge on Feb. 18, 1953, weekly blood cultures remained negative and the patient remained afebrile. Four month follow-up revealed that the patient had resumed normal activity without restriction and had had gradual but complete regression of the vertigo. Blood cultures obtained at bimonthly intervals following discharge for a period of two months remained negative.

Comment. This case presents the problem of an enterococcic subacute bacterial endocarditis developing subsequent to urologic instrumentation in a patient with mitral insufficiency. Unfortunately the patient was subjected to repeated courses of a bacteriostatic agent in the treatment of a "urinary tract infection" without attempt to recover the causative organism and without consideration of the possibility of a blood stream infection. Fortunately she was spared the development of major complications frequently resulting from delay in adequate therapy. Serum bioassay performed following the initiation of the combined therapy revealed that we were able to obtain in vivo blood levels in excess of those shown to be bactericidal in vitro. The method for determining levels for the combined drugs was performed as follows: a specimen of the patient's serum was divided into two parts; to one aliquot enough penicillinase was added to inactivate the serum penicillin and several paper discs were impregnated with this material. The discs were then placed on a culture of *Bacillus subtilis* spores and the resultant zones of inhibition compared with zones of known strength on the same plate. In this manner it was possible to deduce streptomycin activity only. The untreated portion of serum was similarly titrated against the subtilis spores and by comparison with zones of known strengthr it was possible to infer the summative action of the two drugs. Subtraction of the streptomycin level from the combined serum activity level resulted in the approximate penicillin content of the serum.

Case 4. The patient, a 22 year old white female, was initially admitted on Dec. 19, 1952, to the Gynecology Service, Fitzsimons Army Hospital, in a state of shock, delirious, and with temperature of 103 F. Onset of the illness was Dec. 15, 1952, with severe cramping abdominal pain and profuse vaginal bleeding, which terminated on Dec. 16, 1952, with passage of an 8 to 10 week fetus. On December 18, the patient had a temperature elevation and by December 19 had become delirious so she was hospitalized. Past history revealed some question of rheumatic fever at age 6 years, but she had never known of the presence of a heart murmur. Physical examination at the time of admission revealed the patient to be in a state of shock, irrational, and in a semicomatose condition. Blood pressure was 90/30, pulse 120, respirations 22. The significant physical findings included a tense abdomen, minimal vaginal bleeding and a systolic murmur along the left sternal border. Neurologic examination revealed the presence of aphasia, slight nuchal rigidity, sluggish reaction to light of the right pupil. She had some difficulty in turning her eyes conjugately to the right. There was weakness of the right facial muscles and hypalgesia over the entire right side of the body with the tongue protruding to the right. The deep tendon reflexes were hypoactive on the right. Pelvic examination revealed the uterus to be three times normal in size, moveable and tender, with purulent discharge exuding from the external os, which appeared to be widely patent. Laboratory studies revealed a red blood cell count of 1,460,000 and hemoglobin of 4 Gm. per 100 cc.; hematocrit of 20.

Initial therapy consisted of whole blood replacement transfusions with antibiotic therapy consisting of penicillin 200,000 units every two hours and streptomycin 0.5 Gm. twice daily. The patient responded clinically to the whole blood replacement; however, the motor aphasia and meningismus persisted. A spinal tap was performed which was normal except for the presence of 16 lymphocytes and subsequent growth on culture of *Micrococcus pyogenes var aureus*. Culture of the purulent discharge from the external os of the cervix was also positive for *Micrococcus pyogenes var aureus*. The neurologic consultant's impression was thrombosis, probably

venous, of the cortical vein in the left cerebral region, secondary to infection with *Micrococcus pyogenes var aureus*. On December 22, the patient had a temperature elevation to 104.8 F. Streptomycin and penicillin were discontinued and blood cultures were obtained. The patient was started on intravenous oxytetracycline, 500 mg. in 1000 cc. of 5 per cent glucose and distilled water, every 12 hours. On Dec. 25, 1952, the original cultures were reported as positive for *Micrococcus pyogenes var aureus* with sensitivity studies reflecting bacteriostatic effect with chlortetracycline, oxytetracycline and chloramphenicol. The organism was reported as resistant to penicillin and streptomycin. On Dec. 27, 1952, the intravenous oxytetracycline was discontinued, and on December 31 the patient again had a temperature elevation to 104 F. Blood cultures were again obtained and intravenous oxytetracycline was resumed. Five days later the oxytetracycline was again discontinued and the patient started on 20,000,000 units of penicillin daily by continuous intravenous drip, streptomycin, 2 Gm., intramuscularly daily, and probenecid, 2 Gm. daily by the oral route in divided doses. This antibiotic regimen was initiated following report of sensitivity studies which revealed a bactericidal effect at a level of 200 Oxford units of penicillin and 25 micrograms streptomycin per cubic centimeter combined. Other antibiotics tested included neomycin and oxytetracycline singly and in combination with bacitracin, penicillin and streptomycin. These sensitivity studies revealed the organism to be most sensitive to bacitracin, with no growth in a concentration of 1 microgram per cubic centimeter by the tube dilution-plate method. However, in view of the tendency toward nephrotoxicity associated with the use of bacitracin, and the apparent need for rather protracted therapy, the decision was made to treat the patient with the regimen of combined penicillin and streptomycin. On Dec. 28, 1952, the dosage of penicillin was increased to 50,000,000 units daily with dosage of streptomycin and probenecid remaining the same. On Jan. 4, 1953, serum assays were performed revealing 35 micrograms per cubic centimeter of streptomycin and 165 Oxford units of penicillin per cubic centimeter. Subsequent serum assays performed on Feb. 16, 1953, revealed a penicillin level between 150 and 200 units per cubic centimeter and streptomycin level between 10 and 25 micrograms per cubic centimeter. Levels obtained using 50,000,000 units of penicillin, 2 Gm. of streptomycin, and 2 Gm. of probenecid daily did not significantly exceed the concentration in which the organism had been revealed to be sensitive in vitro. However, the effectiveness in vivo was apparently adequate inasmuch as the patient's clinical course continued to improve and the blood cultures subsequent to January 12 remained consistently negative. By March 1 the patient had completed six weeks of antibiotic therapy subsequent to her last positive blood culture and all therapy was discontinued. By March 6 there was no residual neuromuscular involvement. She was discharged from the hospital on March 10, 1953, and was subsequently followed at bimonthly intervals for a period of four months, during which time she remained completely asymptomatic, progressively resuming full activity. Blood cultures obtained during this period were consistently negative.

Comment. In this case of bacteremia due to *Micrococcus pyogenes var aureus*, the antibiotic sensitivity studies revealed that bactericidal levels could be obtained only with massive doses of penicillin combined with streptomycin and with bacitracin. Previous experience (case II) with bacitracin indicated that we could probably not prolong bacitracin therapy beyond three weeks without obtaining nephrotoxicity. Because of the clinical severity of the infectious process it was thought that this would not be an adequate period of treatment. For this reason it was believed that by elevating the penicillin dosage it would be possible to achieve the blood level which had been shown to be bactericidal in vitro. It was further believed that massive dosage of penicillin combined with streptomycin could be continued for an adequate period of time without any danger of toxicity. Moreover, the drug bacitracin constituted a strong weapon to be held in reserve. Unfortunately the in vitro sensitivity levels were not sharply enough delineated between the penicillin level of 125 and 200 units to verify that the in vivo level of 165 units was bactericidal. However, the patient's clinical course demonstrated that this must have been the case. The clinical cure achieved in this case may be attributed to an adequate correlation of in vitro and in vivo data leading to the use of a combination of bactericidal agents in amounts, which in the past would have been considered heroic doses.

Discussion

It would seem appropriate to reiterate for the sake of emphasis certain fundamental concepts and principals which must be considered prerequisite to the improvement of therapeutic results in bacteremias.

In contrast to the existing 70 per cent cure rate in bacteremias, Friedberg[2] has proposed a

90 to 95 per cent cure rate as theoretically possible with the available antibiotics. The discrepancy may be largely attributed to the development of complications, such as heart failure and major embolic accidents resulting from delayed diagnosis, inadequate treatment, or both. Full cognizance must be taken of the fact that a successful outcome depends upon early diagnosis, followed by prompt identification of the infecting agent and administration of appropriate and adequate therapy. It must be emphasized that a complete diagnosis requires accurate identification of the organism and determination of its sensitivity to antibiotics. Hunter[6] has stated, "The central principal of antibiotic therapy of bacterial endocarditis should be the administration of a drug, or combination of drugs, which is the most rapidly and completely bactericidal." Jawetz[2] has likewise stressed that only the in vitro bactericidal action of the antibiotics should be considered, not its bacteriostatic effect. A laboratory method permitting completely accurate and reliable determinations of this in vitro bactericidal action has not as yet been devised. Moreover, it must be recognized that there is not an infrequent lack of correlation between the results of a test for sensitivity to an antibiotic and the effect in vivo. The paper disc method of estimating bacterial susceptibility is satisfactory for most routine screening purposes but it fails to distinguish bactericidal and bacteriostatic effect and moreover is valueless for testing combinations of antibiotics.[7] Foremost emphasis must be placed on one fact: when determination of bactericidal effect is an important factor, as is true in bacteremia, the tube dilution-plate method is indispensable. In spite of its limitations[8] no other method presently available provides the clinician with a more accurate guide to adequate therapy. This is particularly true when dealing with organisms such as the enterococci and staphylococci, different strains of which tend to show considerable variation in their susceptibility to antibiotics.[9] With the assistance of an adequate bacteriologic laboratory, the appropriate antibiotic or combination of antibiotics can be chosen and administered, with due regard to toxic potentialities, in quantities sufficient to attain in vivo the bactericidal effect as delineated in vitro. A valuable corollary guide to the attainment of these in vivo bactericidal levels is also provided by the bacteriological laboratory in the form of serum antibiotic assays, which should be carried out at intervals during the patient's therapeutic course.

In selecting the appropriate antibiotic agent or agents, sensitivity tests may be first carried out on penicillin, streptomycin, chlortetracycline, chloramphenicol and oxytetracycline. The first two drugs belong to Jawetz'[10] group I bactericidal category, the last three drugs belong to the group II bacteriostatic category and are to be avoided as the sole agents of therapy because of the high relapse rate which follows their use.[11] The remaining group I bactericidal drugs, neomycin, bacitracin, and polymyxin may be tested alone or in combination if the organisms prove resistant. Sweet[11] recommends holding these drugs in reserve because of their tendency toward nephro- and neurotoxicity. In general penicillin remains as the most effective and innocuous of the available antibiotic agents. Recent years have witnessed a gradual increase in the empirical criteria for penicillin resistance. The current concept appears to be on the order of a concentration of 10 units per cubic centimeter above which organisms are considered resistant to penicillin. Our experience, and that of others,[12, 13] indicate that massive doses of penicillin combined with an agent such as probenecid permit the attainment of extremely high blood levels of penicillin with relative safety.[14] It is, therefore, recommended that sensitivity studies be carried to high levels, at least 200 units per cubic centimeters, before penicillin is rejected as an effective therapeutic agent in any specific bacteremia, particularly since it is possible to obtain serum levels of at least 2000 units per cubic centimeter. Moreover it is important to bear in mind that sterilization of the blood stream constitutes the ultimate test and should constantly serve as the guide to adjustment in the therapeutic regimen.

In the treatment of staphylococcic bacteremia penicillin is the antibiotic of choice provided an in vivo bactericidal level can be readily attained. Minimum initial dosage should be 20,000,000 units of penicillin daily

or penicillin-resistant staphylococci. Increased erum penicillin levels may be readily attained y giving probenecid 2 to 4 Gm. daily in ivided doses. The addition of streptomycin, 2 o 3 Gm. daily, may frequently produce a aluable synergistic effect. In our opinion herapy should be continued for a period of our to six weeks following the last positive lood culture and the patient observed for an dditional two months. Weekly blood cultures hould be obtained throughout the patient's ospitalization. Reed and Wellman[16] have ecently reported a case of staphylococcic ndocarditis successfully treated with neomycin. The tendency of this drug to produce nephro- and neurotoxicity was manifest in case II, the latter particularly in the form of ototoxicity. The suggested dosage for neomycin is 10 to 14 mg. per kilogram of body weight for chronic administration, but doses of 15 to 20 mg. per kilogram of body weight may be used for only a few days without risk of toxic effect.[17] Bacitracin should also be considered in staphylococcic endocarditis since it is also effective on gram positive cocci. The usual dosage is 50,000 units intramuscularly every 24 hours in divided doses. This drug may be nephrotoxic and the patient should be observed for impairment of renal function or abnormal urinary sediment. With regard to erythromycin, Herrell and associates[18] caution against its routine use in staphylococcic bacteremia because of a tendency toward the development of resistance and the difficulty in obtaining bactericidal levels.

Enterococcal endocarditis constitutes 4 to 10 per cent of cases of bacterial endocarditis in hospital practice.[19] The enterococcus organism is known to be moderately to highly resistant to penicillin. The in vitro effect of penicillin on the enterococcus is primarily one of inhibition.[20] This is paralleled clinically by the fact that enterococcic bacteremia is not cured by penicillin alone. Streptomycin alone is likewise ineffective. However, it has been shown repeatedly, both in vivo and in vitro, that there is an effective synergistic action produced by these agents in combination. The enhanced bactericidal effect has been attributed to the elimination by streptomycin of bacteria partially inhibited but not killed by penicillin.[21] Clinical results have clearly indicated that enterococcic bacteremia can usually be cured by high doses of penicillin plus streptomycin. We would recommend an initial minimum dose of 20,000,000 units of penicillin daily by continuous intravenous drip, 2 Gm. of streptomycin intramuscularly, and 2 Gm. of probenecid daily in divided doses by the oral route. Dosage should be varied as indicated by sensitivity tests, serum levels and clinical response. Therapy should be continued for a period of at least four weeks following the last positive blood culture. Use of the broad spectrum antibiotics, chlortetracycline, oxytetracycline and chloramphenicol has been disappointing with clinical results far inferior to those obtained with penicillin plus streptomycin.

Summary

1. The cure rate of bacteremias has failed to show significant improvement despite an increasing number of available antibiotics. This may be largely attributed to the so-called "resistant" organisms of which staphylococci and enterococci constitute the majority.

2. Experience with four successfully treated cases of this group of gram positive bacteremias is presented and briefly analyzed. Two cases of enterococcic and one of staphylococcic bacteremia responded satisfactorily to massive doses of penicillin combined with streptomycin and probenecid. A case of staphylococcic endocarditis is of particular interest in that the patient was cured with neomycin after all other antibiotics had failed.

3. Certain fundamental principles considered essential to the improvement of therapeutic results are emphasized. The primary aim of therapy should be the administration of a bactericidal agent or agents in sufficient quantity to attain a bactericidal level in vivo and to maintain that level for an adequate period. Thus, the importance of adequate bacteriological control of therapy is evident. Although no completely reliable method of testing antibiotic sensitivity is presently available, the tube dilution-plate method provides the clinician with the most accurate guide to adequate therapy.

4. Specific recommendations regarding the

treatment of both enterococcic and staphylococcic bacteremia are set forth.

Sumario Español

1. El promedio de bacteremias curadas ha dejado de mostrar un aumento significativo no obstante el número aumentado de antibióticos disponibles. Esto se puede atribuir grandemente a los llamados organismos "resistentes", de los cuales estafilococos y enterococos constituyen la mayoría.

2. La experiencia en cuatro casos tratados con éxito con bacteremias Gram positivas de este grupo se presenta y brevemente se analiza. Dos casos de bacteremia enterocócica y uno de estafilocócica respondieron satisfactoriamente a dosis masiva de penicilina combinada con estreptomicina y probenicid. Un caso de endocarditis estafilocócica es de particular interés en que el paciente fué curado con neomicina luego que todos los demás antibióticos fallaron.

3. Algunos de los principios fundamentales considerados esenciales en mejorar los resultados terapeúticos se enfatizan. El objetivo principal en la terapia debe de ser la administración de un agente o agentes bactericidas en cantidades suficientes para obtener un nivel bactericida en vivo y mantener ese nivel por un período adecuado. La importancia de control adecuado bacteriológico en la terapia es evidente. Aunque en el presente no hay ningún método completamente seguro de probar la sensibilidad del antibiótico, el método de tubo y dilución de platicultivo provee al clínico con una guía bastante exacta para la terapia adecuada.

4. Recomendaciones específicas sobre el tratamiento de las bacteremias enterocócicas y estafilocócicas se exponen.

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The Effect of Diphenylhydantoin Sodium (Dilantin), Procaine Hydrochloride, Procaine Amide Hydrochloride, and Quinidine Hydrochloride upon Ouabain-Induced Ventricular Tachycardia in Unanesthetized Dogs

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Ventricular tachycardia has been produced in unanesthetized dogs by the intravenous injection of ouabain, and the ability of various agents to produce reversion to normal sinus rhythm has been tested. Diphenylhydantoin sodium, procaine amide hydrochloride, procaine hydrochloride and quinidine hydrochloride were approximately equally effective; however the procaine hydrochloride effect was shorter and the drug was more toxic than the other three. It is suggested that diphenylhydantoin sodium may merit a trial for the treatment of digitalis-induced ventricular arrhythmias.

THE TOXIC effects of digitalis compounds have been recognized since the time of Withering[1] who first described this agent in 1785. Not until the last three decades, however, has progress been made in the treatment of the toxic cardiac arrhythmias produced by these glycosides. A review has been published by Cohen[2] with an extensive bibliography of experimental and clinical attempts to control these arrhythmias. He describes therapeutic efforts centered around the use of (a) parasympatholytic drugs to combat excess vagal tone, (b) electrolytes, chiefly magnesium and potassium, which have been shown to affect the automaticity of heart muscle, and (c) muscle depressants such as quinidine, procaine, procaine amide, and diethylaminoethanol, which act directly to reduce the irritability and automaticity of the ventricular muscle. Goldberg and Cotten[3] and Zapata Díaz, Cabrera and Méndez[4] have shown that procaine amide may produce temporary reversion of ouabain or digitoxin-induced ventricular tachycardia to normal sinus rhythm. It did not, however, increase the lethal dose of ouabain in cats.[10]

Central nervous system depressants have been reported to be effective in abolishing ventricular ectopic rhythms. Sabathie[5] reported treating 10 cases of ventricular tachycardia (no etiologic data given) with morphine sulfate. The effectiveness of certain general anesthetics against experimentally produced toxic digitalis arrhythmias was shown by Mosey and Stutzman. Gold[7] suggested that sedatives (barbiturates or bromides) might be used for the treatment of ventricular ectopic beats, although not specifically those caused by digitalis compounds. Making the observation that the tissues of the heart and central nervous system responded to many drugs in similar fashion, Harris[8] reported that diphenylhydantoin sodium (Dilantin) caused cessation of ectopic activity in dogs with ventricular tachycardia produced by ligating the anterior descending coronary artery. Since that time he has extended his observations, using this preparation to demonstrate the effects of other antiarrhythmic agents.[9, 10]

The present investigation was suggested by the similarity between the ventricular arrhythmias produced by overdosage of ouabain and those produced by ligating the anterior descending coronary artery in dogs. It was felt that if diphenylhydantoin sodium in reasonable dosage proved effective against ouabain-induced ventricular tachycardia in dogs, it

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might offer promise of clinical usefulness in the prevention or treatment of such arrhythmias.

Methods

Unanesthetized adult mongrel dogs were used in all experiments. The animals were weighed, control electrocardiograms were obtained and 0.08 mg. ouabain per kilogram was injected intravenously. An interval of one hour was allowed for the development of the full effect of the drug. If the animals displayed only auriculoventricular block at this dosage, additional ouabain in doses of 0.01 mg. per kilogram was injected at one-half hour intervals until ventricular tachycardia developed. These arrhythmias have been demonstrated to persist from four to six hours in the absence of therapy directed against them.[6] The total dosage of ouabain ranged from 0.08 to 0.12 mg. per kilogram.

Five therapeutic regimens were tested in five series of animals prepared with ouabain as described above. Ten control animals received 10 per cent glucose in saline intravenously. The other four series were given drugs at the rate of 5 mg. per kilogram per minute intravenously until the arrhythmia reverted to normal sinus rhythm or prohibitive toxicity developed. In 12 animals infused with diphenylhydantoin sodium, the total dose varied from 10 to 30 mg. per kilogram. Five animals treated with procaine hydrochloride required 15 mg. per kilogram. Eight animals infused with procaine amide hydrochloride received a total dose of 10 to 40 mg. per kilogram. Seven dogs were treated with quinidine hydrochloride in doses of 10 to 40 mg. per kilogram.

Continuous electrocardiographic tracings (lead II) were obtained during the infusions and for two minutes thereafter. The stylus of the direct-writing electrocardiograph was kept under constant observation, and additional tracings were taken at suitable intervals until normal ventricular rhythm reappeared or until the time limit for effects of the cardiac glycoside had passed. The criteria of ventricular tachycardia were those recommended by Katz.[11] The criterion for the effectiveness of the drugs tested for antiarrhythmic activity was complete suppression of ectopic activity, demonstrated by electrocardiogram, and lasting for at least two minutes.

Results

Recurrent emesis, beginning approximately five minutes after the intravenous injection of ouabain, was seen in all animals. The dogs became lethargic and unresponsive, reacting very slightly to handling, as the effects of the cardiac glycoside became more pronounced. Control infusions of 10 per cent glucose in saline were without effect upon the ventricular tachycardia. One animal died with ventricular fibrillation from the effects of ouabain, 0.08 mg. per kilogram.

The observations made on the 12 animals receiving diphenylhydantoin sodium are presented in table 1. The electrocardiograms of all animals so treated demonstrated complete cessation of ectopic activity. A dosage of 20 mg. per kilogram was selected arbitrarily, and the first six experiments were done using this dosage. It was observed that in some animals the ventricular tachycardia reverted to normal sinus rhythm before the full dose was given. It was decided, therefore, to administer the minimal effective dose required to obtain normal sinus rhythm in each animal. The last six experiments demonstrate the variability of this dose. The heart rate decreased when the pacemaker shifted upward. Second degree heart block was observed in six animals during the period of effectiveness of diphenylhydantoin sodium, and transient nystagmus was seen in one. There was no evidence of central excitation or respiratory stimulation. In 9 of the 12 animals the electrocardiogram showed a return of ventricular ectopic activity two and one half hours later. Emesis recurred immediately before the reappearance of the ectopic beats in these dogs. Two of the remaining three animals vomited two to three hours after the infusion of diphenylhydantoin sodium. All the animals appeared active and responsive in the interval during which normal sinus rhythm was present, in marked contrast to the lethargy following ouabain. Figure 1 is a detailed graph of one experiment (experiment 4) which demonstrates the characteristic response obtained with diphenylhydantoin sodium. Figure 2 shows tracings of representative electrocardiograms taken during this experiment.

The effects of the other three agents, together with those of diphenylhydantoin sodium, upon cardiac rate and rhythm have been summarized in table 2. The infusion of procaine hydrochloride was uniformly successful in reverting the ventricular tachycardia to an auricular rhythm, producing an auricular

TABLE 1.—*Effect of Diphenylhydantoin Sodium on Ouabain-Induced Ventricular Arrhythmias*

Experiment No. (ouabain dose) mg./Kg.	Diphenylhydantoin sodium dose mg./Kg.	Control heart rate (rhythm)	Heart rate after ouabain (rhythm)	Heart rate after dilantin (rhythm)	Lowest rate after dilantin (rhythm)	Duration of NSR, minutes
1	20	92	210	162	108	40
(0.08)		(NSR)*	(VT)†	(NSR)	(NSR)	
2	20	124	168	122	107	40
(0.08)		(NSR)	(VT)	(NSR)	(NSR)	
3	20	116	224	188	88	¶
(0.08)		(NSR)	(VT)	(NSR)	(NSR)‡	
4	20	84	230	180	96	30
(0.08)		(NSR)	(VT)	(NSR)	(NSR)	
5	20	124	225	190	105	¶
(0.08)		(NSR)	(VT)	(NSR)	(NSR)	
6	20	92	228	140	60	60
(0.09)		(NSR)	(VT)	(NSR)	(NSR)‡	
7	25	116	228	152	68	120
(0.08)		(NSR)	(VT)	(NSR)	(NSR)	
8	10	104	228	88	42	35
(0.09)		(NSR)	(VT)	(NSR)	(NSR)§	
9	20	96	236	148	80	180
(0.08)		(NSR)	(VT)	(NSR)	(NSR)	
10	10	124	212	172	120	20
(0.08)		(NSR)	(VT)	(NSR)	(NSR)‡	
11	15	96	208	92	64	¶
(0.08)		(NSR)	(VT)	(NSR)	(NSR)‡	
12	30	88	232	128	76	40
(0.08)		(NSR)	(VT)	(NSR)	(NSR)‡	

* NSR is normal sinus rhythm.
† VT is ventricular tachycardia.
‡ Occasional auriculoventricular block.
§ Occasional ventricular extrasystoles.
¶ No return of ventricular ectopic activity in 3 hours.

tachycardia of short duration. One animal developed convulsions and subsequently died following the infusion. The other four dogs manifested central nervous system excitation and tremor.

The procaine amide hydrochloride results were similar to those obtained with diphenylhydantoin sodium. Ventricular ectopic activity was abruptly terminated. Second degree auriculoventricular block was observed in two instances. One animal receiving ouabain in a dosage of 0.09 mg. per kilogram developed ventricular tachycardia which terminated in cardiac standstill. Stimulation of the heart by massage through the chest wall resulted in the establishment of a bizarre ventricular arrhythmia. Infusion of 10 mg. of procaine amide hydrochloride per kilogram produced cardiac arrest. The animal was again revived, but died approximately 24 hours later. Electrocardiograms taken before death showed auricular

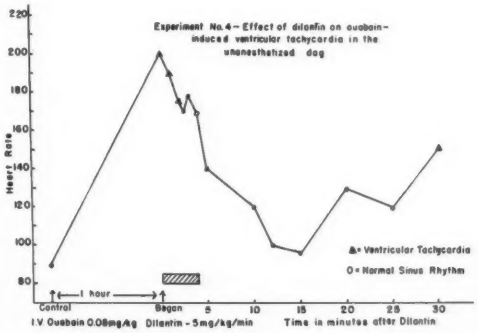

FIG. 1. The effect of diphenylhydantoin sodium on ouabain-induced ventricular tachycardia in the unanesthetized dog.

standstill with an idioventricular rate of 28 per minute.

Of the seven animals given quinidine hydrochloride in minimal effective dosage, reversion to sinus rhythm occurred in five. The remaining two animals developed convulsions at dosages

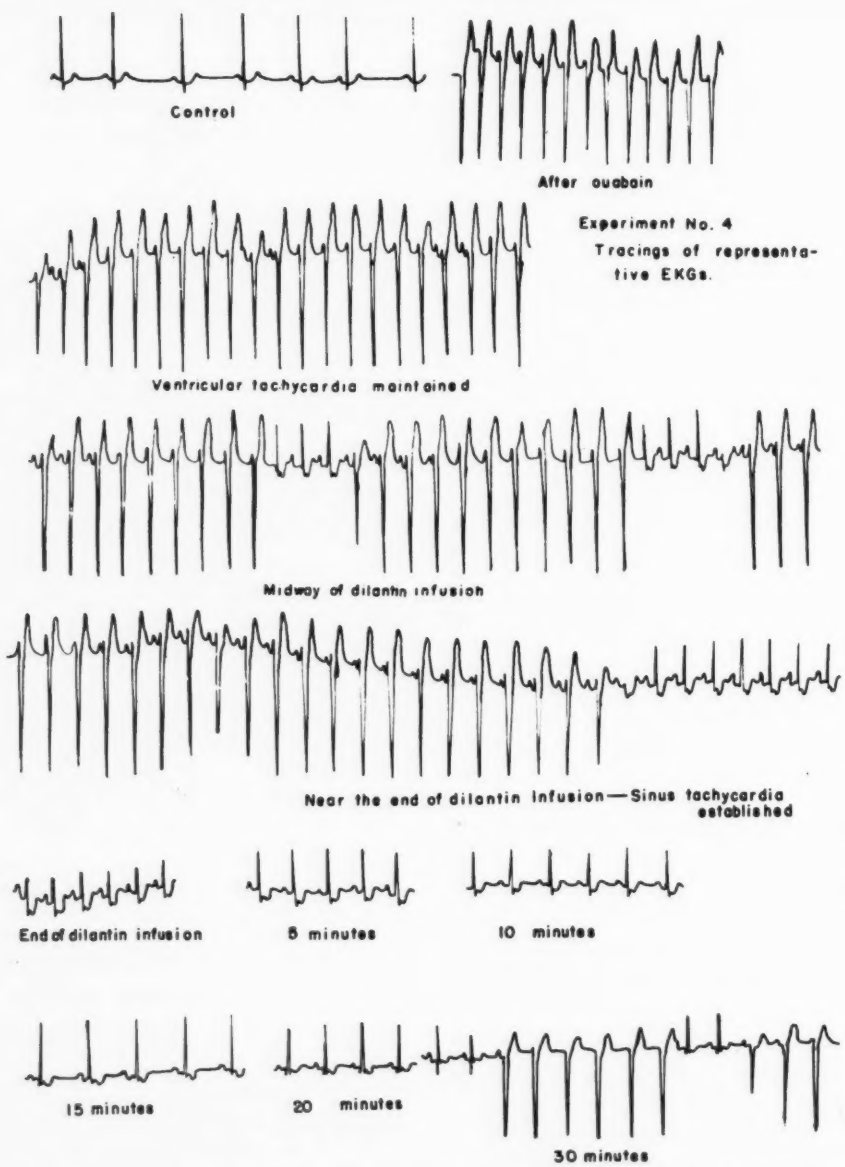

FIG. 2. Representative electrocardiograms taken during the experiment illustrated in figure 1.

of 35 and 40 mg. per kilogram, respectively, without any apparent effect upon the ventricular arrhythmia. Evidence of central nervous system excitation, consisting of increased irritability and tremor appeared in two other dogs. During the infusion one animal developed ventricular flutter which terminated abruptly with the establishment of a predominantly sinus rhythm which subsequently became regular.

The heart rate observed after treatment differed statistically from the rate taken before ouabain administration only in the case of procaine hydrochloride. There was no statistical

TABLE 2.—*Effects of Various Agents upon Ouabain-Induced Ventricular Tachycardia in Dogs*

Drug	Reversion to NSR*			Maximum Effect		Recurrence of VEA†		
	No. Reverted / No. Treated	Heart Rate‡ Mean / S.D.§	Time Minutes Mean / S.D.	Heart Rate Mean / S.D.	Time Minutes Mean / S.D.	No. Recurring	Heart Rate Mean / S.D.	Time Minutes Mean / S.D.
Procaine hydrochloride	5/5	202 ±54.9	2.0 ±0.5	173 ±64	8 ±6.2	4	188 ±24.2	14 ±5.8
Procaine amide hydrochloride	7/8	135 ±47.3	3.0 ±1.6	99 ±52.6	14 ±9.3	6	185 ±9.1	30 ±38.4
Quinidine hydrochloride	5/7	208 ±32.4	2.0 ±1.3	106 ±52.6	6.0 ±2.1	4	168 ±16.2	23 ±15.5
Diphenylhydantoin sodium	12/12	149 ±33	5 ±1.7	89 ±25.2	32 ±15.2	9	151 ±15.7	64 ±49.7

* NSR means normal sinus rhythm.

† VEA means ventricular ectopic activity.

‡ Mean heart rate 33 dogs before ouabain 104 ± 13.8. Mean heart rate 32 dogs after ouabain 215 ± 14.2.

§ S.D. means standard deviation.

All times are minutes from the beginning of the intravenous infusion of the drug.

difference in the duration of action of procaine amide hydrochloride, quinidine hydrochloride, or diphenylhydantoin sodium in the dosages used in these experiments.

DISCUSSION AND CONCLUSIONS

The data obtained in this investigation indicate that diphenylhydantoin sodium was effective in dogs in abolishing the ventricular tachycardia resulting from toxic overdosage with ouabain. Procaine hydrochloride, procaine amide hydrochloride and quinidine hydrochloride also proved effective in the treatment of these ventricular arrhythmias. The duration of action of procaine hydrochloride was much shorter than that of the other three agents, thus confirming clinical experience in the use of this drug. Qualitatively similar results were obtained with procaine amide hydrochloride, diphenylhydantoin sodium and quinidine hydrochloride. Procaine hydrochloride seemed to have less effect than the other agents in slowing the heart rate in these experiments. This difference may be related to the strong central stimulation observed after the infusion of procaine hydrochloride.

Toxic manifestations attributable to diphenylhydantoin sodium were confined to one instance of transient nystagmus. Harris[8] reported mild emesis immediately after infusion of diphenylhydantoin sodium in three of his animals. No such effect was seen in the present experiments. No evidence of central excitation was seen following the infusion of either diphenylhydantoin sodium or procaine amide hydrochloride in contrast to the marked central nervous system stimulation occurring in all animals receiving procaine hydrochloride and in four of the seven animals receiving quinidine hydrochloride. While the number of experiments is too small to permit definite conclusions, the data suggest that the toxicity of diphenylhydantoin sodium is no greater than that of procaine amide hydrochloride and

TABLE 3.—*Comparison of Clinical and Experimental Dosage of Agents Effective against Ventricular Arrhythmias*

Drug	Clinical Doses mg./Kg.	Experimental Doses mg./Kg.	No. Successes/ No. Treated
Quinidine	5–20	10	3/3
		20	2/3
		40	0/1
Procaine amide	Maximum of 20	10	3/4
		20	3/3
		40	1/1
Diphenylhydantoin sodium	5–10	10	3/3
		20	7/7
		30	2/2

is probably less than that of either procaine hydrochloride or quinidine hydrochloride.

The relationship of nausea and vomiting to the cardiac toxicity produced by the cardiac glycosides has been investigated in the past. It has been suggested that emesis is dependent upon a reaction within the heart, which, in turn, reflexly or centrally stimulates vomiting. In the present series of experiments, the emetic effect of ouabain was decreased during the period of diphenylhydantoin sodium activity, and, without exception, vomiting heralded the return of ventricular ectopic activity.

Comparison of the dosage range utilized in these experiments with the dosage employed clinically is presented in table 3. The dosage for diphenylhydantoin sodium was computed on the basis of that tolerated for chronic administration in the control of seizures. The close correlation of the doses used in this study with those employed clinically suggests that the method might be used to evaluate agents for effectiveness against ventricular ectopic activity.

Summary

Diphenylhydantoin sodium, procaine hydrochloride, procaine amide hydrochloride and quinidine hydrochloride were effective in abolishing the ventricular tachycardia resulting from ouabain overdosage in unanesthetized dogs. Although the effects of these agents were qualitatively similar, procaine hydrochloride was found to have less bradycardic action, shorter duration of effect and greater toxicity than the other three drugs.

The close correlation of the doses found effective in these experiments with the doses used clinically suggests that this method might prove useful in testing new compounds for their effectiveness in counteracting ventricular hyperirritability.

Sumario Español

Difenilhidantoína sódica, clorhidrato de procaína, clorhidrato de amida procaína y clorhidrato de quinidina fueron efectivos en abolir la taquicardia ventricular resultante de dosis excesiva de ouabaína en perros no anestesiados. Aunque los efectos de estos agentes fueron cualitativamente similares, el clorhidrato de procaína se encontró tener menos acción bradicárdica, efecto de duración menor y mayor toxicidad que las otras drogas.

La correlación de la dosificación hallada efectiva en estos experimentos con la dosificación usada clinicamente, sugiere, que este método puede probar ser de utilidad en la prueba de compuestos nuevos en cuanto a su eficiencia en contrarrestar la hiperirritabilidad ventricular.

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The Value of the Atrial Electrokymogram in the Diagnosis of Mitral Regurgitation

Observations on Patients with Rheumatic Mitral Stenosis before and after Mitral Valvuloplasty

By FELIX G. FLEISCHNER, M.D., WALTER H. ABELMANN, M.D., AND ROBERT BUKA, M.D.

The difficulty of correct clinical assessment of the functional state of the diseased mitral valve has prompted this re-evaluation of the atrial electrokymogram in 15 patients with rheumatic mitral disease. By means of a technic stressing careful placing of the pick-up device and recording from multiple locations along the left atrial border, a pattern characteristic of mitral regurgitation could be demonstrated. In general, the electrokymographic predictions correlated well with the operative findings.

THE diagnosis of mitral insufficiency, correct as to presence and degree, has gained greater significance since the advent of the surgical treatment of mitral stenosis.[1, 2, 3] A slight or moderate degree of insufficiency not infrequently accompanies mitral stenosis and does not prevent the improvement resulting from valvuloplasty.[4, 5] However, a number of instances have been reported where the operation was undertaken on the assumption that mitral stenosis was present either as the sole or the dominant lesion, but where a high degree of insufficiency was found.[4-7]

The present communication attempts to evaluate the reliability of electrokymograms in the diagnosis of mitral insufficiency by correlation with the findings at subsequent valvuloplasty. The difficulties and limitations of the clinical diagnosis of mitral regurgitation, which have been discussed at length in a previous communication,[5] justify this.

Atrial dilatation under normal and pathologic conditions results in outward movement of the atrial wall. Fredzell and co-workers[8] in their studies on filling and emptying of the left atrium by rapid serial roentgenography during angiocardiography, emphasize that the left atrium is similar to a sphere. Therefore contraction and dilatation occur in a rather concentric fashion, and there is little chance for paradoxical movement of parts of the wall such as may occur in more irregularly shaped chambers. The normal atrial movements have been observed by fluoroscopy, by classic roentgenkymography and more recently by electrokymography.

The normal electrokymographic tracings of the left atrium, as described by Luisada, Fleischner and Rappaport[9] and confirmed by various authors,[10-13] consist of a slow rise of the curve during ventricular systole, preceded by a sharp negative wave in presystole (inward motion caused by atrial contraction) and interrupted by a more rounded negative wave in early systole (inward motion caused by lowering of the A-V septum, only partly compensated by venous inflow into the atrium). According to general convention, the polarity of the recording apparatus is arranged in such a way that an outward movement of the border of the cardiac silhouette registers as upward deflection of the curve.

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This work was done, in part, during Dr. Abelmann's tenure of a Research Fellowship of the American Heart Association.

Mitral insufficiency produces regurgitation of blood during systole, resulting in a sudden distention of the left atrium. This systolic distention, if marked, can be recognized by fluoroscopy.[5, 14-16] This abnormal distention was first identified graphically by means of roentgenkymography by Heim de Balzac and Pannier,[17] and has been analyzed electrokymographically by Luisada and Fleischner[18] and many others.[10, 12, 13, 19-22] The typical pattern of mitral insufficiency consists of a rapid rise during isometric contraction and in early systole, followed by a horizontal line which may be straight, notched, or convex, and lasts throughout systole. Opening of the mitral valve is followed by a rapid fall of the tracing. This is the pattern which we[18] have called the "positive systolic plateau." It should be emphasized, however, that the rapid early systolic rise of the tracing is the essential characteristic of the regurgitation pattern as discussed in more detail in a later paragraph.

The systolic positive plateau of the electrokymographic tracing is quite similar to Wiggers' left atrial volume curve in experimental mitral regurgitation in the animal,[23] and resembles closely the left atrial pressure curves obtained in patients with mitral regurgitation by Munnell and Lam[4] and by Wynn and coworkers.[24] Most of the quoted authors emphasize the specificity of the "positive systolic plateau" of the atrial border tracing and have not found this sign in individuals with normal hearts. There are a few discordant opinions, however. Dussaillant and collaborators[25] reported patterns of systolic expansion in occasional atrial border electrokymograms of normal subjects.* Similarly, Soloff, Zatuchni and Stauffer[26] found a positive systolic plateau in 10 out of 15 healthy subjects. One of the present authors (W. H. A.)[5] reported less specificity of the positive plateau in a previous study, performed, however, with less satisfactory technic.

Thus the method of atrial electrokymography merits discussion in some detail.

* Recently, Dussaillant and associates reported that when several points of the left atrium of normal subjects are studied, a pattern suggesting systolic expansion is found only in an exceptional tracing.[28]

Method and Material

Methodologic Requirements. In our opinion a satisfactory method for electrokymography of the left atrium must meet the following requirements:

1. Simultaneously with the electrokymogram, the cardiac cycle must be recorded in a manner which will permit accurate timing. This is done best by recording the electrocardiogram as well as the phonocardiogram. A good phonocardiogram may suffice, while a carotid pulse tracing renders accurate timing more difficult. The difficulty one of us (W. H. A.) previously encountered with this technic[5] is probably in part attributable to the fact that only a carotid tracing was available for timing of the events in the cardiac cycle.

2. The slit must be placed with the utmost care.

3. Tracings of the aorta, pulmonary artery, and ventricles should be obtained in order to facilitate detection of effects of superimposition or summation in a presumed left auricular tracing.

4. Records should be taken at both a slow and a fast paper speed. The fast speed facilitates accurate correlation of the events in the kymogram with the phases of the cardiac cycle. The slow speed, on the other hand, may facilitate recognition of general characteristics and summation effects. This may be illustrated by the following case, one of several similar observations.

J. G., a 26 year old male, was a healthy medical student. Clinical, roentgen and electrokymographic findings were entirely normal. The first border tracing of the left atrium in the right oblique position shows a typical arterial pattern apparently owing to superimposition of the descending aorta or hilar arteries, the pulsations of which eclipse the atrial pulsation. The tracing taken with high speed (75 mm. per second) demonstrates the great similarity of the assumed atrial tracing with the tracing of the aortic knob, while a slow tracing (25 mm. per second) simulates a "positive systolic plateau" (fig. 1).

5. Multiple tracings must be taken from the outline of the left atrium in order to obtain a representative sample of atrial border motion and minimize the misinterpretation of superimposition and summation in a single tracing.

6. Recordings obtained in positions where superimposition of the descending aorta or hilar vessels cannot be avoided or tracings which suggest other irregularities not accounted for should be used with reservation or discarded entirely.

Method Used: The following technic has been adopted for the present study. The Sanborn Electrokymograph and Tri-Beam Cardiette provided simultaneous records of the heart sounds, electrokymogram and electrocardiogram (usually lead II). The subjects were examined in the sitting position. In the posteroanterior view, the point of opposite pulsation on the left, "the third curve" as called by us, and on the right, the position "right atrium high"

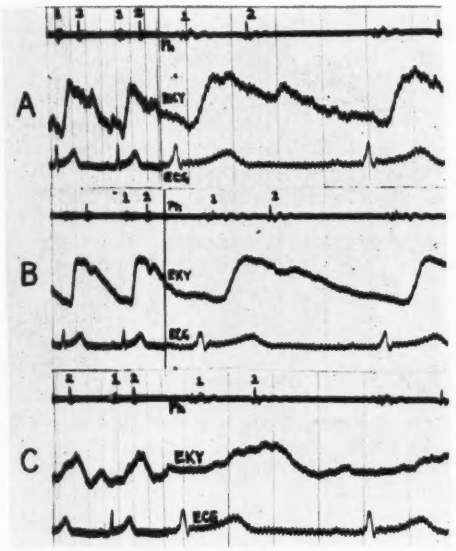

FIG. 1. Healthy male, age 26. (*A*) Left atrial border tracing, high, right anterior oblique. (*B*) Aortic Knob. (*C*) Left atrial border tracing, right anterior oblique, 2 cm below tracing *A*. Each strip shows phonocardiogram, electrokymogram and electrocardiogram, in this order. In the slow speed tracing, top left, the curve simulates the "systolic plateau" of mitral regurgitation. The fast speed tracing, top right, however, reveals the similarity with the aortic tracing, bottom right. Tracing *A* thus is the summation effect of the weak atrial and the superimposed stronger descending aortic pulsation. The normal atrial pattern in tracing *C* demonstrates the value of tracings from multiple sites.

which represents the site of potential projection of a large left atrium, were chosen for recording. In this view, the standard tracings of the apex, pulmonary artery, aortic knob, and "right atrium low" were also taken. The left atrial border, furthermore, was recorded in the right anterior oblique position in three places, high, mid and low, and similarly in the left anterior oblique position, high, mid and low. Thus a minimum of six and a maximum of eight border tracings of the left atrium were obtained. The "third curve" was not obtainable in instances without sufficient bulge of the left atrial appendage or postoperatively, and "right atrium high" did not record the left atrium when this did not project on the right side. In order not to rely entirely upon border movement, we placed the slit of the pick-up device in such a way that we included this border eccentrically, having the greater portion of the slit over the body of the atrium, thus obtaining a fair amount of densography of the atrial body at the same time. All leads were recorded at both 25 mm. per second and 75 mm. per second paper speeds.

Case Material

In addition to numerous previous studies on normal subjects where only two or three tracings of the posterior wall of the left atrium were obtained, five healthy medical students served as controls for this extended schedule with three tracings of the posterior atrial wall in both right and left anterior oblique positions.

Fifteen patients with rheumatic mitral valvular disease were studied. All had an apical diastolic murmur characteristic of mitral stenosis. Of these, 11 showed no evidence of mitral regurgitation by history, physical examination, electrocardiogram, x-ray films and fluoroscopic examination of the heart.

Patient 8 showed a grade 2 apical systolic murmur, left axis deviation by electrocardiogram, right ventricular hypertrophy and marked left auricular enlargement with systolic expansion on fluoroscopy; these findings were interpreted as indicative of at least moderate regurgitation. Patients 11 and 12 were suspected of mild regurgitation on the basis of grade 2 apical systolic murmurs. Patient 14 was suspected of mild to moderate regurgitation on the basis of a grade 2 systolic murmur at the apex and an electrocardiogram showing left axis deviation.

All 15 patients subsequently underwent mitral valvuloplasty, and 10 were studied again postoperatively.

Interpretation of Electrokymograms

A. Tracings in the presence of normal sinus rhythm. The presystolic downward deflection in the atrial kymogram in patients with *mitral stenosis* and normal sinus rhythm is frequently seen to be rather pronounced (fig. 2). This apparent change in the downward deflection of greater amplitude and duration than in normal tracings, as stressed by Andersson,[27] is probably a consequence of the preceding delayed and abnormally slow fall of the curve during early diastole signalizing impaired atrial emptying. Two factors may contribute to this delayed contraction of the left atrium, namely delayed evacuation of the atrium due to resistance of the narrow mitral ostium and accelerated refilling of the atrium from the reservoir of the engorged pulmonary veins. Increased pulmonary venous pressure may also be responsible for faster atrial filling after atrial contraction which is suggested by a rapid rise of the curve often seen immediately following the accentuated fall in presystole. This rise may coincide with the period of isometric contraction of the ventricle and may be misinterpreted as evidence of mitral regurgitation. The following upward surge in early systole, however, is less steep than that of mitral regurgitation.

We consider a left atrial tracing indicative *of*

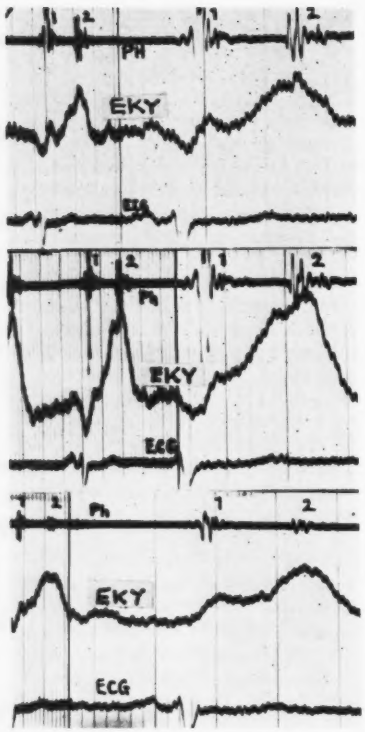

FIG. 2. Case 2. C. T. Pure mitral stenosis. Norma sinus rhythm. Three tracings of the posterior wall of the left atrium in right anterioroblique position, high, middle, and low, each with phonocardiogram, (top), electrokymogram, (middle), and electrocardiogram (bottom). The strips showing records with slow (25 mm./second) on the left and fast (75 mm./second) motion on the right are arranged below each other in such a way that the QRS complexes of the first cycle in fast recording are aligned in a vertical line. Line interval equals 0.04 second. The top and middle tracings show a deep presystolic wave: forceful atrial contraction. All three tracings show the normal slow expansion of the atrium during systole.

mitral regurgitation when a rapid rise occurs during the period of isometric ventricular contraction or early during the period of rapid ventricular ejection reaching a peak early during systole. This is followed by a horizontal line which may be straight, slightly sloping upward or downward, or convex. The early systolic negative wave caused by the ventricular pull is often completely effaced or noticeable as a small notch (fig. 3*A*). In rare instances a rapid early systolic rise may be followed by a slower fall during late systole. We consider this tracing as of doubtful evidence of mitral regurgitation (fig. 3*B*). Whenever the upward movement reaches its peak after the

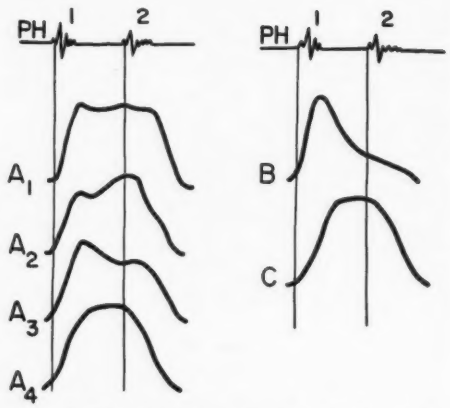

FIG. 3. The electrokymographic border tracings of the left atrium in mitral regurgitation. Diagram. The top graph represents the heart sounds (1 and 2); A_1, A_2, A_3 and A_4, characteristic tracings of mitral regurgitation showing rise (expansion), followed, A_1 by a positive systolic plateau; A_2, by a small notch and a slow rise; A_3, by a slow slope; A_4, by a dome. B is interpreted as regurgitation in early systole only. C slower rise in early systole, probably caused by superimposed arterial motion; not diagnostic of mitral regurgitation.

first third of systole, the tracing is not considered to indicate mitral regurgitation (fig. 3*C*).

B. Tracings in the presence of atrial fibrillation. Mitral stensosis produces no characteristic signs in the absence of atrial contraction, while the signs of mitral regurgitation are the same as with normal sinus rhythm (fig. 4).

Interpretation of Operative Findings

The electrokymographic findings were compared to the anatomic diagnosis made by the surgeon at the time of cardiotomy. The surgeon's diagnosis is based upon the size of the mitral valve area during systole and diastole and takes into consideration the absence or presence and degree of a regurgitant jet, as felt by the finger inserted into the left auricle. While the surgeon's diagnosis has great advantages over a diagnosis based on clinical data or on autopsy findings, especially with regard to the degree of functional closure or competence of the valve during systole, it also has definite limitations which have been discussed previously.[5, 16] While the area of the mitral valve may be estimated in this manner with a high degree of accuracy, the detection of a regurgitant jet is a function of its size, form and direction as well as of the sensory threshold of the finger, which is raised by the glove. Furthermore, during cardiotomy the blood pressure usually is lower than normal and may be very low, in which case regurgitation may be minimal even with a structurally

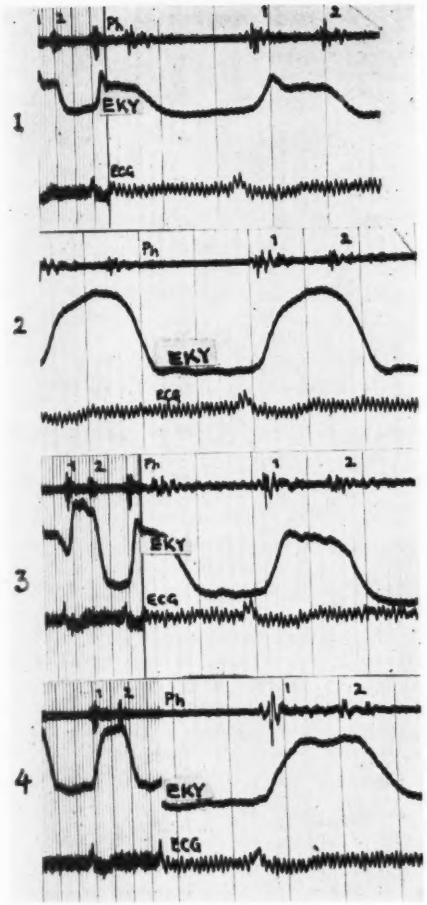

FIG. 4. Case 8. H. F. Mitral insufficiency. Atrial fibrillation. Border tracings of the left atrium in similar arrangement as figure 3. (1) Position "right atrium high" = left atrium prominent on the right: "sloping plateau." (2) Left atrium in right anterior oblique high: "dome shaped positive curve." (3) Left atrium in right anterior oblique low: "sloping plateau. (4) Left atrium in left anterior oblique middle: "positive systolic plateau."

incompetent mitral valve. Not enough emphasis has been placed upon the fact that opening of the chest disturbs the normal physiologic conditions in several respects. The flopping pulsation of the heart in the presence of pneumothorax or pneumopericardium has been observed roentgenologically long ago. If the lung with its damping effect is replaced by free air, the ventricle swings with bigger amplitude. The same must occur when the chest is opened. It is not as yet evident which additional role is played by the changed position of the diaphragm, the opening of the pericardium and the exposure of the veins and atria to atmospheric pressure instead of the changing lower pressures within the closed chest.

Furthermore, arrhythmia favors the occurrence of mitral regurgitation. In runs of bigeminy one may observe mitral regurgitation during the second beat of the couple, not discernible at normal sinus rhythm. According to Wiggers,[23] the fraction of the tidal volume that flows back into the left atrium is larger when the myocardium is depressed. These and possibly other factors make it plausible that observations of the function of the mitral valve at the time of operation may differ from those made with the chest closed and the patient under more normal conditions. Notoriously, in contradistinction to mitral stenosis, mitral insufficiency is greatly dependent upon the functional condition of the heart and the circulatory dynamics, and thus the amount of regurgitation is subject to momentary fluctuations.

RESULTS

Normal Subjects

Auricular electrokymograms taken in five normal subjects showed consistently normal patterns. In no instance was the picture suggestive of mitral regurgitation.

Patients with Mitral Valvular Disease

I. The Preoperative Examination. In the presence of *normal sinus rhythm*, the electrokymographic diagnosis was arrived at in the following manner: If the pattern of mitral regurgitation (any of tracings A), was present in one or two tracings, mild mitral regurgitation was assumed, designated *mr* in the tables. If three to five of the tracings showed this pattern, a moderate degree of mitral regurgitation was diagnosed, *mR*. More than five positive tracings were considered to signalize marked mitral regurgitation, *MR*. This admittedly is an arbitrary and incomplete classification kept so strict for the purpose of objective evaluation of the method. In clinical practice we relate these findings to the size of the left atrium. A certain volume of regurgitating blood may produce an outward movement of the atrial wall of considerable amplitude when the atrium is small. The same amount of blood flowing back into a grossly dilated atrium may cause a small or even subliminal outward movement.

The analysis of the electrokymographic tracings is presented in table 1. Table 2 shows

TABLE 1.—*Analysis of the Border Electrokymogram of the Left Atrium*

Case No.	Age and Sex	Rhythm	Status	Individual Electrokymographic Leads								Electrokymographic Diagnosis of Regurgitation
				3d Curve	Right Atrium High	Left Atrium						
						RAO			LAO			
						1	2	3	1	2	3	
1. C. S.	38F	NSR	Preop.	1S	1		3			S		Moderate
			Postop.	0	1?	0	0	0	0	3	0	? Minimal
2. C. T.	28F	NSR	Preop.	S		0	S	0	0	0	0	None
			Postop.			0	0	0	3	S	S	None
3. B. L.	19F	NSR	Preop.	S	0	0	0	0	0	0	0	None
			Postop.	0		0	0	S	0	0	0	None
4. A. H.	43F	NSR	Preop.	0		0	0	0	0	S	0	None
			Postop.	3	0	1	1	1?	0	S	0	Mild to moderate
5. E. S.	40F	NSR	Preop.	0		0	2	2	S	S	0	Mild
			Postop.	0	0	0	0	0	0	1?	0	? Minimal
6. M. L.	44F	NSR	Preop.	S	0	0	1?	0	0	0	1?	Mild
7. G. D.	31F	NSR	Preop.	S	0	0	0	1?	0	0	0	? Minimal
8. H. F.	43M	AF	Preop.	1	1	1	1	1	3	1	3	Marked
9. T. G.	46M	AF	Preop.	0	0	0	3	1	3	0	1–2	Mild
			Postop.	0	0	3	2	0	0	1	0	Mild
10. M. G.	24M	AF	Preop.		1	0	3	1	1	0	1	Moderate
			Postop.	0	1	1	2	2	1	1	1	Moderate to marked
11. F. G.	38F	AF	Preop.	0		1	1	1	0	2	0	Moderate
			Postop.	0	0	3	0	0	3	0	0	None
12. H. L.	28F	AF	Preop.	0	0	0	2?	0	3	1?	1	Moderate
			Postop.	0	1?	1	1	?	1?	0		Moderate
13. E. D.	52F	AF	Preop.				1	1	1	1		Moderate (old, 1948)
			Postop.		0	0	0	0	0	0	0	None
14. G. M.	44F	AF	Preop.	0	0	0	2	0	2	2	0	Mild
15. C. R.	44F	AF	Preop.	0	0	0	0	1	1	2	0	Mild

"S" stands for deep presystolic negative wave, indicative of mitral stenosis. "1" stands for positive systolic plateau typical of mitral regurgitation; "2" for early systolic expansion; "3" for insignificant late systolic plateau, as explained in figure 3; "0" for normal tracings or insignificant changes.

RAO = Right Anterior Oblique. LAO = Left Anterior Oblique.

the correlation of the electrokymographic diagnosis with the clinical and operative findings. From this listing, it will be seen that the agreement of the electrokymographic and surgical diagnosis was satisfactory in the seven patients with normal sinus rhythm. In the only case where there was disagreement (case 1) the electrokymogram suggested mitral stenosis with some regurgitation, but no regurgitant jet was felt at cardiotomy. However, the mitral valve area was slightly larger than usual in tight mitral stenosis, and the systolic blood

TABLE 2.—*Electrokymographic Diagnoses and Findings at Cardiotomy*

Case No.	Age and Sex	Rhythm	Electrokymographic Diagnosis*		Findings At Cardiotomy§					Blood Pressure Preop.
			Preop.	Postop.	Valve Type†	Valve Area (cm²)	Regurgitation Before Valvuloplasty	Regurgitation After Valvuloplasty	Blood Pressure	
1	38F	NSR	MS mR	N	IA	1.0	0	0	60/	100/60
2	28F	NSR	MS	N	IIA	0.6	0	0	80/40	108/70
3	19F	NSR	MS	MS	IA	0.7	0	0	95/	96/50
4	43F	NSR	MS	mR	IA	0.8	0	0	70/50	110/60
5	40F	NSR	MS mr	N	IA	0.6	?	0	70/50	130/78
6	44F	NSR	MS mr		IIA	0.7	+	+	65/	130/80
7	31F	NSR	MS		I–IIA	0.3	0	0	70/45	108/70
8	43M	AF	MR		IB	2.0	(+++)‡		0	128/70
9	46M	AF	mr	mr	IA	1.2	0	0	110/	130/80
10	24M	AF	mR	MR	IIA	0.8	0	0		120/65
11	38F	AF	mR	N	I–IIA	0.7	0	+	90/	130/80
12	28F	AF	mR	mR	IIB	0.8	+	0	100/	85/60
13	52F	AF	mR	N	IIA	0.8	0	0	80/	115/70
14	44F	AF	mr		IA	0.5	0	0	90/	124/80
15	44F	AF	mr		IA	1.0	+	+	64/	110/80

* MS = mitral stenosis; mr = mild mitral regurgitation; mR = moderate mitral regurgitation; MR = marked mitral regurgitation.

† Type I: rigid valve with marginal leaflet fusion and, usually, calcification. Type II: flexible funnel fusion of leaflets. Group A: mitral orifice pointing toward ventricular wall. Group B: mitral orifice pointing into outflow tract. (Harken and colleagues.[3])

‡ Postmortem; operative death.

§ The electrokymographic diagnosis was unknown to the surgeon.

pressure was only 60 at the time of intracardiac palpation. Moreover, at the time of operation and before the heart was opened, the left atrium exhibited visible systolic expansion.

In the presence of *atrial fibrillation*, tracings permit no comment as to the presence of mitral stenosis. The electrokymographic diagnoses of mitral regurgitation, when compared with the operative findings, were satisfactory in four of the eight patients with atrial fibrillation. In the remaining three, (cases 10, 11, and 13) the degree of mitral regurgitation was probably overestimated (table 1).

The only patient who on preoperative evaluation showed a pattern of mitral regurgitation in all leads (case 8) was found to have marked mitral regurgitation as predicted from the electrokymogram.

II. The Postoperative Atrial Electrokymogram. In 10 patients, electrokymographic examinations were repeated one to two months after mitral valvuloplasty. The atrial electrokymogram became normal in five cases (cases 1, 2, 5, 11, 13), four of which had shown regurgitation preoperatively. The tracings remained unchanged in four cases (cases 3, 9, 10, 12), and suggested mitral regurgitation induced by the operation in one case (case 4, fig. 5).

One may raise the question whether the postoperative electrokymographic changes are any measure of the success of the operation in terms of correction or mitral stenosis and/or production of mitral regurgitation. On the basis of the present material, this question cannot be answered.

COMMENTS

The problem of assessing the degree of mitral regurgitation present in a patient with mitral valve disease may be viewed from two perspectives. The experimental physiologist may express the volume of regurgitated blood either absolutely per beat or minute, or relatively as a percentage of the total forward flow through the mitral valve. No method is known today to fulfill these demands in man under normal

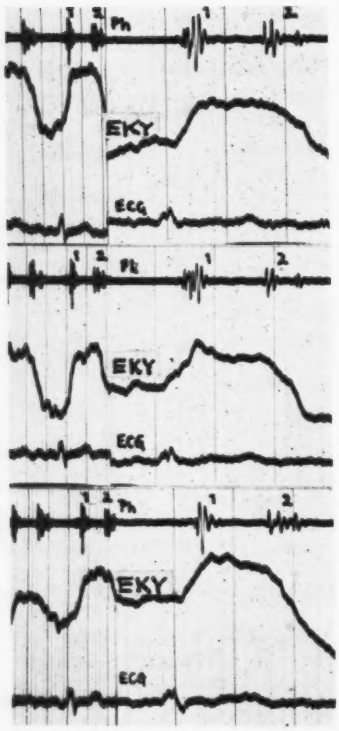

FIG. 5. Case 10. M. G. Atrial fibrillation. Postoperative electrokymogram indicating marked mitral regurgitation. Three border tracings of the left atrium in left anterior oblique arranged as in figure 3. All three, high, middle, and low, show presystolic onset of a steep rise with a typical positive systolic plateau. Considering this graphic evidence, it is difficult to accept as final the surgeon's statement that there is no mitral regurgitation.

conditions. Hence, the accuracy of the electrokymographic findings cannot be absolutely validated. The problems facing the clinician, fortunately, do not require as rigorous an exactitude. The particular questions in evaluating a patient with mitral valve disease are: (1) Is there mitral insufficiency (alone or in addition to known mitral stenosis)? (2) If so, is it "significant", that is, regurgitation of a degree which would contraindicate operative treatment of stenosis, or affect adversely the postoperative prognosis?

It seems that the presence of mitral regurgitation can be established with a fair degree of accuracy by electrokymography. The theoretic-physiologic rationale and the practical experience of many authors support the value of this method. Very isolated observations in the literature of a "false positive" tracing may be due to individual circumstances of technic or clinical condition. We are not aware, however, that mitral regurgitation if present did not manifest itself in the electrokymogram (no "false negatives").

As to the second question, further long range follow-up observations on patients who have undergone valvuloplasty are required before one can determine how much regurgitation is "significant." On the other hand, methods are desirable to assess the degree of regurgitation before operation in order to make such followup studies meaningful. For the present, then, we have classified the findings as signalizing mild, moderate, or marked regurgitation. It appears reasonable to accept the operative findings of a regurgitant jet as evidence of regurgitation. If a jet is strong, it may be safe to conclude that regurgitation must be at least moderate during normal life. If the jet is weak, the level of the systolic blood pressure and the area and type of the mitral valve as palpated may give clues as to the probable severity of regurgitation during normal life. The tendency, however, is likely to be toward underestimation rather than overestimation of regurgitation by the palpatory method.

On the other hand, the operative findings being regarded as yardstick, overdiagnosis by electrokymography is to be expected, especially in cases where no jet is felt by the surgeon and the electrokymographic diagnosis of mild regurgitation is based on some definite abnormal tracings among others that are normal. In no instance of the present series was mitral regurgitation encountered at operation without having been predicted from the electrokymogram, nor was regurgitation ever of higher degree than predicted. Thus, while electrokymography may prevent the unexpected encounter with high grade mitral insufficiency, the validation of electrokymography in respect to the positive diagnosis of mild degrees of regurgitation will have to await comparison

with a method of physiologic quantitation of regurgitation which is not subject to the limitations of the observations at cardiotomy.

The fluoroscopic observation of the atrial outward movement was rather reliable when the left atrium projected considerably on the right side; in other instances, the agreement was only fair, with errors in either direction if we apply the electrokymographic findings as yardstick.

The clinician will now ask: What can the electrokymogram add to the conventional clinical preoperative evaluation? In the present group of patients, selected for mitral valvuloplasty, a fully adequate clinical diagnosis was possible in all but one patient. In this case (case 8) mitral regurgitation was considered moderate clinically, marked by electrokymography, and actually found predominant at postmortem examination. This was the only patient in this series who could not have been benefited by mitral valvuloplasty. Thus in the occasional patient with clinically unsuspected predominance of mitral regurgitation, the electrokymogram may give the warning signal.

Summary and Conclusions

Electrokymograms of the left atrium were taken in five normal subjects and in 15 patients with rheumatic mitral valvular disease, 10 of whom were re-examined after mitral valvuloplasty. The need for precise technic, accurate timing of the cardiac cycle, and multiple atrial tracings was emphasized.

Some abnormal atrial tracings were seen in all patients with rheumatic mitral disease, none in the healthy control subjects.

With the surgeon's observation of a regurgitant jet during cardiotomy accepted as a base for comparison, the electrokymographic diagnosis of absence, presence or degree of mitral regurgitation showed a fair consistency. This was almost complete in patients with normal sinus rhythm, while in those with atrial fibrillation the electrokymogram tended to slightly "overdiagnose" mitral regurgitation. In no instance, however, was mitral regurgitation found to be of higher degree at operation than had been predicted by electrokymography.

After mitral valvuloplasty, the atrial electrokymogram became normal in five patients, four of whom had shown electrokymographic evidence of regurgitation preoperatively. The tracings remained unchanged in four, and suggested mild mitral regurgitation in one.

It is concluded that with careful technic atrial electrokymography may be a valuable adjunct to the preoperative evaluation of the degree of mitral regurgitation in patients with rheumatic mitral disease.

Acknowledgment

We wish to thank Drs. Howard Frank, Dwight E. Harken, George W. Starkey, and John W. Strieder for the opportunity to study their patients and to use their records. We are very grateful to Drs. Laurence B. Ellis and Aldo A. Luisada for their helpful suggestions in the editing of this paper.

Sumario Español

Se obtuvieron electroquimogramas del atrio izquierdo en 5 sujetos normales y en 15 pacientes con enfermedad reumática de la válvula mitral, 10 de los cuales fueron reexaminados luego de valvuloplastía mitral. La necesidad de técnica precisa, determinación exacta del tiempo en el ciclo cardíaco y trazados atriales múltiples se enfatizan.

Algunos trazados atriales anormales se observaron en todos los pacientes con enfermedad reumática mitral, ninguno en los sujetos controles normales.

Con la observación del cirujano de un chorro regurgitante durante la cardiotomía aceptado como una base para la comparación, el diagnóstico electroquimográfico de ausencia, presencia o grado de regurgitación mostraron una consistencia favorable. Esto fué casi completo en los pacientes con ritmo sinuatrial, mientras en aquellos con fibrilación atrial el electroquimograma tendió ligeramente a "sobre diagnosticar" regurgitación mitral. En ningun caso, sinembargo, se encontró la regurgitación mitral ser de un grado mayor durante la operación que lo que predijo el electroquimograma.

Luego de la valvuloplastía mitral, el electro-

quimograma se tornó en normal en cinco pacientes, cuatro de los cuales habían mostrado evidencia electroquimográfica de regurgitación preoperatoriamente. Los trazados permanecieron sin cambiar en cuatro y sugirió regurgitación mitral ligera, en uno.

Se concluye que con una técnica cuidadosa la electroquimografía atrial puede ser un aditamento valioso para la evaluación preoperatoria del grado de regurgitación mitral en pacientes con enfermedad reumática mitral.

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Lack of Correlation between Rales and Arterial Oxygen Saturation in Patients with Pulmonary Congestion and Edema

By Albert Vitale, M.D., Paul R. Dumke, M.D., and J. H. Comroe, Jr., M.D.

It is generally believed that pulmonary edema impairs the diffusion of oxygen from alveoli to pulmonary capillary blood and produces anoxemia. However, some patients who apparently have widespread pulmonary edema, as judged by the extent of rales heard over the lung fields, still have normal arterial oxygen saturation. Explanations are advanced for the lack of correlation between extent of rales and arterial oxygen saturation.

IT IS generally agreed that pulmonary congestion, per se, does not lead to arterial anoxemia. However, it is widely believed that pulmonary edema is associated with an impairment in the diffusion of oxygen from the alveolar gas into the pulmonary capillaries, and as a consequence leads to anoxemia. During the past five years, we have measured arterial oxyten saturation in 40 patients with congestive heart failure and pulmonary edema. We have been impressed by the poor correlation between the arterial oxygen saturation and severity of the pulmonary edema as judged by the extent of rales heard over the lungs. We wish to describe these studies briefly and suggest several possible explanations for the lack of correlation.

Since there is at present no accepted objective and quantitative method for measuring pulmonary capillary congestion or pulmonary edema in man, the patients were selected on the basis of their physical findings and medical record. All had heart disease, dyspnea at rest or on exertion and rales easily audible at least over the lung bases. In so far as was possible on the basis of clinical judgment, patients with pulmonary disease were excluded. In more than half of the cases, chest x-ray films were made within five hours of the study, and all patients with radiologic evidence of pleural effusion or pulmonary disease were excluded. No pulmonary function studies were performed; since many of the patients included in this study were in the fifth to eighth decades, it is likely that pulmonary function was slightly impaired in some instances.[1]

The study consisted simply of a careful auscultation of the chest for rales, followed by the withdrawal of arterial blood for measurement of oxygen saturation[2] while the patient was breathing room air. Rales were graded as follows: Bilateral basal = 1; bilateral, over lower one half of chest = 2; bilateral, over three fourths of chest = 3; and bilateral, throughout all lung fields = 4. All patients with grade 4 rales had acute pulmonary edema.

Results and Discussion

Figure 1 shows the data obtained. It is not surprising that some of the patients with only grade 1 or grade 2 rales had low arterial oxygen saturations because (a) some of these patients may have had pulmonary disease in addition to congestive heart failure, and (b) some may have had interstitial pulmonary edema which could impair the diffusion of oxygen without leading to the production of rales. However, it is surprising that 7 of the 12 patients with acute pulmonary edema and with bubbling rales

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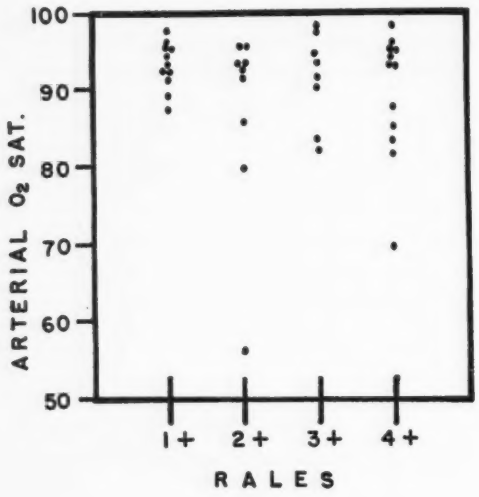

FIG. 1

audible over all lung fields had arterial oxygen saturation greater than 93 per cent.*

Two explanations may be offered: (1) A slight to moderate impairment of diffusion or a reduction in the diffusing capacity of the lungs does not necessarily lead to a reduction in arterial oxygen saturation in the resting patient. Figure 2 is a diagrammatic representation of a possible explanation for this. Ordinarily, with a normal alveolar-capillary membrane, mixed venous blood comes into almost complete equilibrium with the alveolar oxygen tension about one fourth the way along the course of the pulmonary capillary (curve 1) so that full oxygenation is achieved by a low mean oxygen gradient between the alveolar gas and capillary blood. With progressive impairment of diffusion (curves 2, 3, and 4), full oxygenation is delayed until, in curve 4, it is just barely achieved at the very end of the pulmonary capillary. With more severe impairment of diffusion, even the end-pulmonary capillary blood will not become fully saturated (curve 5) and anoxemia occurs even with the patient at

* In our laboratory, normal values for arterial oxygen saturation for young men are 97.4% ± 2.1 and for men older than 50 years are 96.5% ± 1.7%.

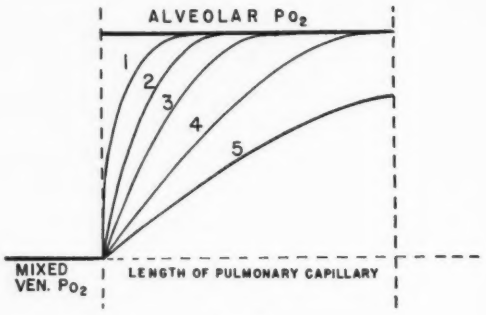

FIG. 2

rest in bed. One of the important reasons for making the more complex measurement of the diffusing capacity of the lungs is to detect those cases which have impaired diffusion but still have normal arterial oxygen saturation.

(2) Pulmonary edema is not necessarily a diffuse process impairing diffusion in all alveoli. It is quite possible that a major problem in pulmonary edema is that of airway obstruction produced by distribution through the airways of edema fluid formed in one or two regions of the lung. If this be true, blood flow through the obstructed or poorly ventilated areas must be rerouted in some cases to the nonobstructed, well-ventilated areas of the lungs so that edema seems to originate in many areas of the lungs simultaneously without the occurrence of severe anoxemia.

SUMMARY

Arterial oxygen saturation was measured in 40 patients with heart disease, all of whom had rales of varying extent. There was little correlation between the arterial oxygen saturation and the diffuseness of rales. In seven patients with acute and apparently widespread pulmonary edema, arterial oxygen saturation was greater than 93 per cent. Several explanations are suggested.

SUMARIO ESPAÑOL

La saturación arterial de oxígeno se determinó en 40 pacientes con enfermedad cardíaca, todos los cuales tenían estertores en variable extensión. Hubo poca correlación entre la

saturación arterial de oxígeno y la difusión de los estertores. En siete pacientes con edema pulmonar aguda y aparentemente difusa, la saturación arterial de oxígeno fué mayor de 93 por ciento. Algunas explicaciones se sugieren.

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Ventricular Function

V. The Circulatory Effects of Aramine; Mechanism of Action of "Vasopressor" Drugs in Cardiogenic Shock

By Stanley J. Sarnoff, M.D., Robert B. Case, M.D., Erik Berglund, M.D. and L. Charlotte Sarnoff

The cardiovascular effects of a new, long-acting, sympathomimetic amine, Aramine, are described. Cardiac output, aortic pressure, coronary flow, and ventricular stroke work rise while atrial pressures fall. A sustained increase in myocardial contractility is produced and the myocardium does not require more coronary flow per unit of ventricular work after its administration. The circulatory effects of ventricular failure produced by restricting coronary flow are reversed by the drug. The authors seriously question the premise that the ideal agent for the management of cardiogenic shock should act solely on the peripheral vascular bed.

THE increased use of so-called vasopressor agents in the treatment of cardiogenic shock indicated the desirability of achieving a more complete understanding of the circulatory effects of this type of drug. One such agent, Aramine [levo-1-(m-hydroxyphenyl)-2-amino-1-propanol], is the subject of the experiments to be described below. The focusing of attention on this drug by Beyer resulted from that worker's investigation on the relation of chemical structure to pharmacologic function in a series of aromatic amine compounds.[1]

Aramine has a relatively long-lasting effect after a single dose, is effective by oral, intramuscular or intravenous administration, and appears to be innocuous as regards cardiac arrhythmias. Previously it has been thought to exert its pressor effect solely by influencing the peripheral vascular bed. However, earlier observations in this laboratory suggested that it has a significant myocardial effect as well.[2, 3] In late hemorrhagic shock, Aramine produced a marked increase in coronary flow and a fall of the elevated left atrial pressure.[3] Further studies suggested that the drug increased the survival rate of dogs subjected to oligemic hypotension.[4]

The objectives of this communication will be to demonstrate: (1) the effect of Aramine on atrial and arterial pressures, cardiac output, coronary flow and peripheral vascular resistance; (2) the effect of the drug on ventricular function (myocardial contractility) as well as its effect on the systemic vascular bed; (3) the effect of Aramine on coronary flow requirements per unit of ventricular work; (4) the drug's effect on the hypotension and low cardiac output induced by coronary insufficiency. An attempt will also be made to indicate why a "vasopressor" agent is more likely to be therapeutically effective in cardiogenic shock if it also increases myocardial contractility.

For the purpose of clarity it is best to define the term myocardial contractility as used herein. It is quantitatively described by the relationship between ventricular filling pressure and the stroke work of that ventricle throughout the range of its function.[5]

Method

1. General. The methods used were similar to those described in previous publications.[5, 6] The experiments were done in anesthetized (morphine-chloralose-urethane) open-chest dogs with a complete circulation. Briefly, they involved the continuous electrical recording of (a) pressures in the left and right atria and the pulmonary artery and aorta.[7] (b) the total systemic blood flow with the Potter Electro-

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Dr. Case is a Fellow of the United States Public Health Service.

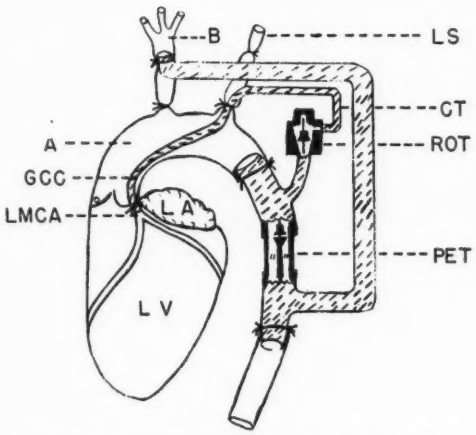

FIG. 1. Schematic drawing of the technic used for measuring systemic and left main coronary artery blood flow. LA = left atrium. LV = left ventricle. A = aorta. PET = Potter electroturbinometer. ROT = rotameter. CT = coronary tubing. GCC = Gregg coronary cannula. LMCA = left main coronary artery. B = brachycephalic artery. LS = left subclavian artery. The sum of flow through PET and ROT = cardiac output (minus right coronary artery flow).

turbinometer,*[8, 9] and (c) the flow through the left main coronary artery by means of a modified Gregg cannula and the recording rotameter of Shipley and Wilson.[10] A reservoir connected to one femoral vein permitted the infusion of blood or dextran† so as to change the ventricular filling pressures in a step-wise fashion. Ventricular stroke work was calculated as the product of the stroke volume and mean arterial minus mean atrial pressure. Full ventricular function curves (figs. 4*a* and 6*a*) were thus obtained. Resistances were calculated according to Green and expressed in millimeters of mercury pressure drop per cubic centimeter of flow.[11]

The Aramine was rapidly injected in doses ranging from 0.01 to 0.11 mg. per kilogram either into a femoral vein or into a cardiac catheter with its tip in the inferior vena cava. The solution used was 0.5 mg. per cubic centimeter made up freshly from a 1 per cent solution in ampoule form.‡

2. Technic for Time Dissociation of Systemic and Cardiac Effect of Drugs. Figure 1 is a schematic representation of a part of the preparation. With such an arrangement the immediate effects of the intravenous injection of a rapidly acting agent can be differentiated in time and analyzed as regards its systemic and cardiac effects. For, after the drug arrives at the left ventricle and is ejected from it, it rapidly reaches the periphery and exerts its effect thereon (systemic effect). It also enters the right coronary artery immediately. In order to reach the left coronary artery, the drug in the meanwhile must traverse the coronary tubing-rotameter-cannula circuit, and only then does it affect the myocardium (cardiac effect). The time interval between the arrival of the drug at the periphery and at the myocardium is determined by the volume of the coronary circuit and the rate of flow through it. Further, the duration of the interval between the onset of the systemic and cardiac effects can be adjusted by varying the volume of the tubing between the rotameter and coronary cannula.

RESULTS

1. Effect of Repeated Intravenous Doses of 0.01 mg. per Kilogram on the Arterial Pressure and Pulse Rate. In figure 2*A*, *B* and *C*, Aramine was injected in doses of 0.01 mg. per kilogram at two-minute intervals until a total of 0.1 mg. per kilogram had been given. With the dog already slightly hypertensive and the vagi intact (fig. 2*A*), the elevation of arterial pressure following this dosage schedule was slight (from a mean of 121 to 138 mm. Hg). The predominant effect was a bradycardia, which, presumably by reflex mechanisms, limited the elevation of arterial pressure. Figure 2*B* shows the effect of this same dosage schedule after the mean arterial pressure had been lowered to 62 mm. Hg by hemorrhage. Under these circumstances the pressure rose substantially (from 62 to 145 mm. Hg) and the pulse rate slowed appreciably only after the dog's pressure had returned towards the control level as a result of giving the drug. The effect of the same dosage schedule after vagotomy is shown in figure 2*C*. The reflex bradycardia having been eliminated by vagotomy, a substantial pressor effect (from a mean of 154 to 240 mm. Hg) was obtained. The data for figures 2*A*, *B* and *C* were obtained from the same dog over a seven-hour period, approximately three hours intervening between *A* and *B*, and *B* and *C*. The blood that was removed between *A* and *B* was returned between *B* and *C*.

* Supplied through the courtesy of Mr. David M. Potter, Potter Aeronautical Co., Newark, N. J.

† Supplied through the courtesy of Mr. J. Martin of the Commercial Solvents Corporation, New York City.

‡ Supplied through the courtesy of Dr. Karl H. Beyer, Sharp & Dohme, West Point, Pa.

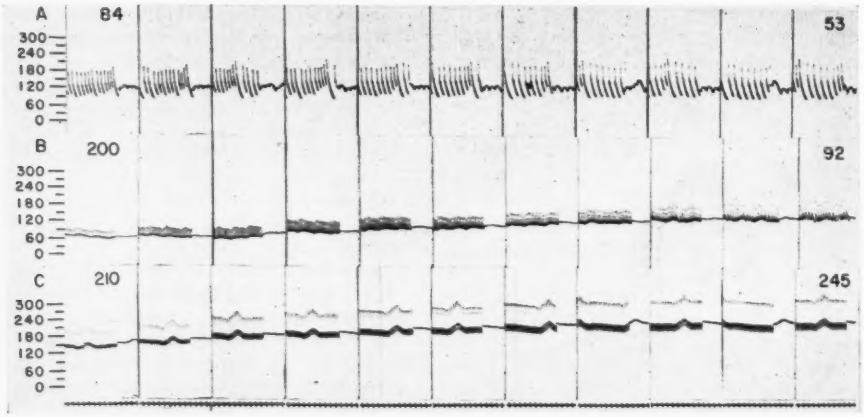

FIG. 2. *A*, *B* and *C* show the effect on femoral artery pressure and pulse rate of 0.01 mg. per kilogram Aramine given intravenously 10 times at two-minute intervals. Experiment 94. Morphine-chloralose-urethane anesthesia. Chest unopened. Scale at left in millimeters of mercury. Numbers at beginning and end of *A*, *B* and *C* are heart rates. In *A*, the vagi are intact. In *B*, the vagi are intact but the arterial pressure had been lowered and the pulse rate increased by hemorrhage. In *C*, the blood removed before *B* had been reinfused and the vagi cut. Three hours intervened between *A* and *B* and between *B* and *C*. See text.

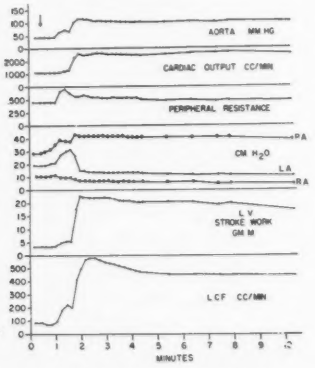

FIG. 3. Circulatory effects of 0.03 mg. per kilogram Aramine. Experiment 82. Dog weight 24.0 Kg. Aramine given intravenously at arrow. PA = pulmonary artery. LA = left atrium. RA = right atrium. LCF = left main coronary artery flow. Left ventricle stroke work in grammeters. Note the fall in RA during initial rise in LA. See figure 1 and text.

2. The Hemodynamic Effects of Aramine. The administration of Aramine to the vagotomized dog in doses up to 0.05 mg. per kilogram was followed by an increase in cardiac output, left main coronary artery flow and aortic and pulmonary artery pressures. Right and left atrial pressures fell, the left more than the right. The administration of additional amounts of Aramine, which brought the total to 0.11 mg. per kilogram, elevated aortic pressure and coronary flow further but had only a slight further effect on atrial pressures and cardiac output.

The direction of the changes just described was consistent. The relative change of each value, however, varied considerably with the cardiovascular state being studied. When the control hemodynamic values were within the normal range, the decline of atrial pressure after Aramine was relatively small. When, however, failure was present (as evidenced by a high atrial pressure and a low cardiac output and aortic pressure) the decline of atrial pressure was a prominent part of the response. One such experiment is shown in figure 3. Changes similar to those shown in figure 3 were obtained in the same dog 19 minutes earlier as the result of giving one microgram per kilogram of norepinephrine (Levophed) intravenously. The only significant difference was the transient character of the norepinephrine response. The dog studied in figure 3 was anemic, the hematocrit being 23.7 per cent, thus accounting for the high coronary blood flows recorded.[12]

The hemodynamic result of a large dose of

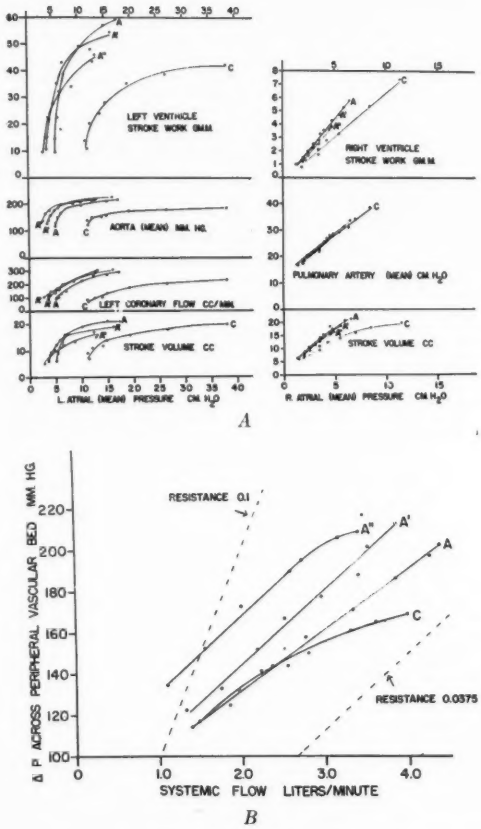

FIG. 4 *A*. Four successive ventricular function curves simultaneously for the right and left ventricles. Experiment 92. Dog weight 15.8 Kg. C = control curve. A = curve after 0.03 mg. per kilogram Aramine intravenously. A′ = curve after total of 0.06 mg. per kilogram. A″ = curve after total of 0.11 mg. per kilogram. Left ventricle stroke work, mean aortic pressure, left main coronary artery flow and stroke volume are all plotted against the mean left atrial pressure in centimeters of water on the left. Right ventricle stroke work, pulmonary artery pressure and stroke volume are plotted against mean right atrial pressure on the right.

B. Same experiment as in 4 A. Pressure difference (ΔP) across peripheral vascular bed in mm. Hg plotted against systemic blood flow in liters per minuts. *C*, *A*, *A′*, and *A″* same as in 4*A* above. Broken lines are constant resistance lines.

Aramine (more than 0.15 mg. per kilogram) in the vagotomized dog was a marked increase in aortic pressure, no significant increase in cardiac output and no change or a moderate

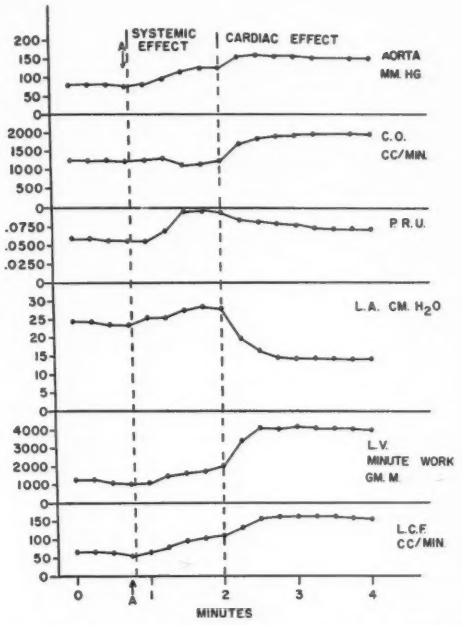

FIG. 5. Time dissociation of the effect of Aramine on the peripheral vascular bed and the myocardium. Experiment 74. Dog weight 19.0 Kg. See text and figure 1. At the arrow marked A 0.1 mg. per kilogram Aramine was injected through a catheter with its tip near the right atrium. Volume of rotameter-tubing-cannula circuit shown in figure 1 was 125 cc.

rise in left atrial pressure. This was a consequence of the intense peripheral vasoconstriction which, by producing very high aortic pressures, masked the cardiac effect.[5] See below.

3. Effect of Aramine on Right and Left Ventricular Function Curves; Differentiation of Myocardial and Systemic Effects by Graded Dosage. Full ventricular function curves were obtained in the control state and after the injection of doses of Aramine totaling 0.03, 0.06 and 0.11 mg. per kilogram. Figure 4*A* shows the effect of these doses on the right and left ventricular function curves. After 0.03 mg. per kilogram there was a marked increase in myocardial contractility. Additional doses of 0.03 and 0.05 mg. per kilogram did not greatly alter myocardial contractility.

The changes in peripheral vascular resistance and tone which occurred with these injections are shown in figure 4*B*. Peripheral resistance

was not increased with the first injection of 0.03 mg. per kilogram (except at high flows) but was substantially higher throughout the entire range after the subsequent injections.

4. Differentiation of Systemic and Cardiac Effects of Aramine by the Time-Dissociation Technic. Figure 5 shows the effects of 0.1 mg. per kilogram of Aramine on the systemic vessels and the myocardium. This dog was in myocardial failure as evidenced by the high left atrial pressure and low left ventricular work. Following the injection of Aramine through a right atrial catheter there was a period of about 75 seconds during which the effects shown were due solely to systemic vasoconstriction. During this period (systemic effect), aortic pressure rose while cardiac output fell slightly; simultaneously, peripheral resistance increased sharply, left atrial pressure rose to even higher levels, left ventricular work increased somewhat and coronary flow was also elevated. At the second dotted line a sharp break in the trend of values occurred (cardiac effect). Cardiac output rose substantially thereby producing a further increase in aortic pressure. Left ventricular work rose to almost 400 per cent of its original value while left atrial pressure declined markedly. Simultaneously, coronary flow also rose to appreciably higher levels. This increase in work with the decrease in filling pressure is strong presumptive evidence that the administration of

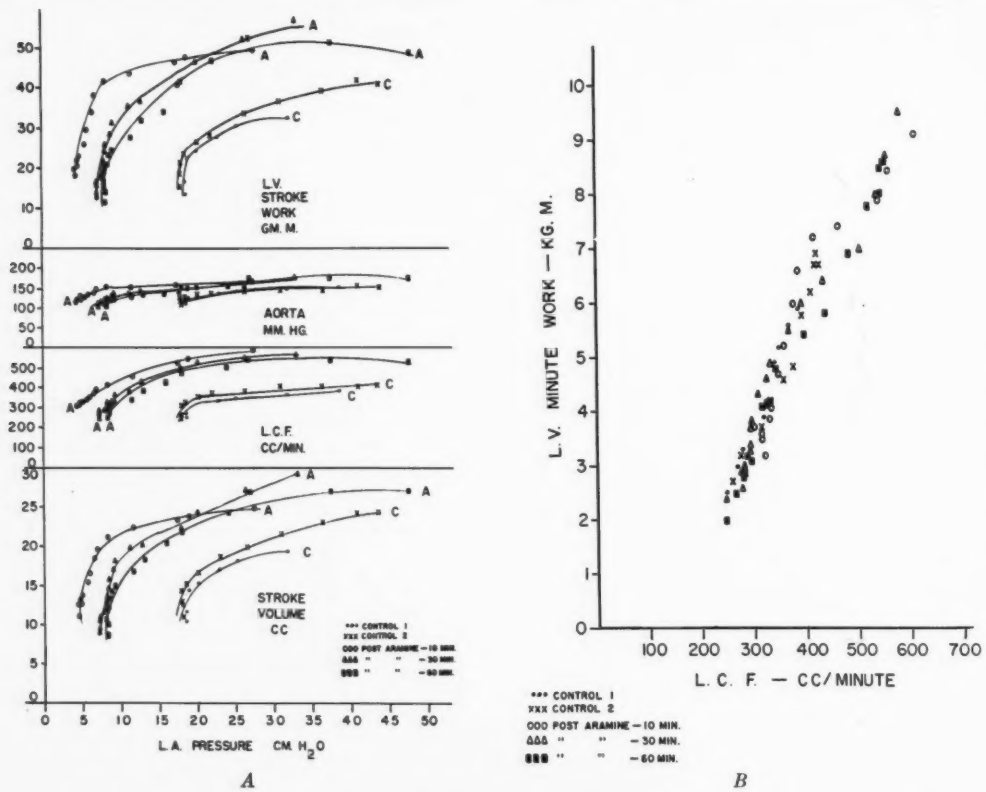

FIG. 6*A*. Experiment 83. Dog weight 29.8 Kg. Five left ventricular function curves. The two labeled *C* are control curves. The three curves labeled A were obtained 10, 30 and 60 minutes after the intravenous injection of 0.05 mg. per kilogram of Aramine.

B. Same experiment as in 6*A*. Left ventricular work per minute in kilogram meters plotted against left main coronary artery flow in cubic centimeters per minute.

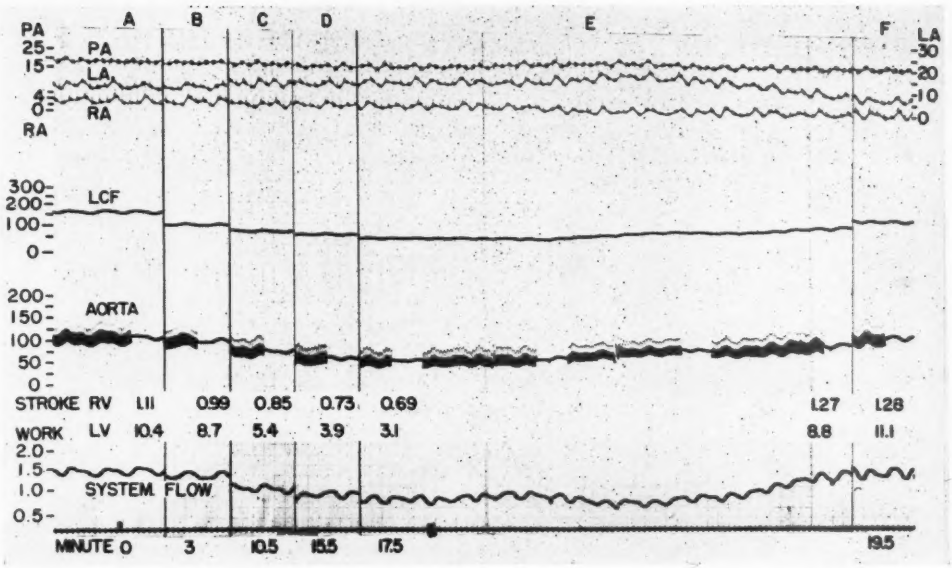

FIG. 7. Tracing showing the circulatory effects of induced left main coronary artery insufficiency and the subsequent injection of Aramine. Experiment 93. Dog weight 26.0 Kg. In the top channel are the pulmonary artery, left atrial and right atrial pressures in centimeters of water. PA and RA scale at the left; LA scale at the right. Second channel = left main coronary artery flow in cubic centimeters per minute. Third channel = aortic pressure in millimeters of mercury, both full pulse and mean pressures. Inserted between the third and fourth channels are the calculated right (RV) and left (LV) ventricular stroke work in gram meters. Fourth channel = systemic blood flow in liters per minute. Time signal in seconds. Numbers at bottom = minutes after start of tracing. Screw-clamp on tube feeding the left main coronary artery was tightened after *A* and slightly further after *B*. No further adjustment of screw clamp which remained in place thereafter. At the signal at the bottom at the beginning of *E*, 0.03 mg. per kilogram Aramine injected through cardiac catheter. Note the time-dissociation effect. See text.

the drug had, by a direct action on the myocardium, placed the ventricle on a much more favorable Starling or ventricular function curve.[5] (See fig. 4*A* and 6*A*.)

It might be felt that in this instance left ventricular function improved only because of the increased coronary flow that immediately preceded the cardiac effect. That this is not the case is indicated by the fact that two minutes prior to the injection of Aramine shown in this figure, mechanical coronary perfusion at a rate of 257 cc. per minute for one and one-half minutes had failed to produce a similar salutary effect.

5. Effect of Aramine on the Ventricular Function Curve of the Failing Ventricle. More complete information about the effect of Aramine on the failing heart was revealed by examining the full range of ventricular function before and after its administration. Further, it seemed desirable to know at least a minimal duration of time that this effect of the drug lasted. The left ventricular function curves obtained from a dog in a moderate degree of myocardial failure, that is, high left atrial pressures for the stroke work obtained is shown in figure 6*A*. Two control curves were obtained before and three curves, 10, 30 and 60 minutes after the intravenous injection of 0.05 mg. per kilogram of Aramine. Simultaneous left main coronary flows, aortic pressures and stroke volumes are also shown. Left ventricular function was strikingly improved by the drug and this lasted for at least one hour. Longer periods were not studied.

6. Coronary Flow Requirements per Unit of Left Ventricular Work Before and After Aramine. From the data in figure 6*A* a plot

was made of the coronary flow per minute against left ventricular work per minute. This data, shown in figure 6*B*, indicates that the heart did not require a greater coronary flow for any given work output after Aramine. Coronary arteriovenous oxygen differences were not obtained in this experiment, but in other experiments it was shown that the increased oxygen requirement of the heart is normally met by an increase in the coronary flow, not by increased oxygen extraction.[13] This suggests that the oxygen requirement as well as the coronary flow requirement per unit of work was no greater after the Aramine than before it.

7. The Effect of Aramine on the Arterial Hypotension and Low Cardiac Output of Coronary Insufficiency. After the usual preparation was completed, a control period was obtained (fig. 7*A*). Following this a screwclamp on the tubing to the left main coronary artery was tightened until the aortic pressure, cardiac output and stroke work fell in the face of a rising left atrial pressure (fig. 7*B* to *E*). It may be presumed that at this stage the coronary vessels could not dilate further as a result of myocardial hypoxia; at least they did not dilate sufficiently to permit coronary blood flow to keep up with the requirements of the left ventricle. Then, with the coronary screw clamp still in place, 0.03 mg. per kilogram Aramine was injected intravenously (at the signal in the beginning of *E*). This was followed by a fall in left atrial pressure and a rise in coronary flow, arterial pressure, cardiac output and stroke work to or near their control levels. Note the time dissociation effect.

8. Summary of Data. A comparison of ventricular function curves before and after Aramine was done in eight dogs and in three of these left main coronary artery flow was also measured as shown in figure 4*A*. In one dog the Aramine had little cardiac effect even in high doses. It was of interest that this dog's heart was also refractory to epinephrine, the potency of which was subsequently verified on another dog. In the other seven dogs the Aramine produced a significantly higher left ventricular function curve. Of the five dogs in which right ventricular function curves were obtained a higher curve was found after Aramine in three.

The type of time dissociation of myocardial and systemic effects shown in figures 3, 5 and 7 was observed 22 times in 10 dogs.

Discussion

The use of multiple ventricular function curves is probably the most precise means presently available for quantitating the effect of an intervention on the myocardium.[5] The data presented above demonstrate that Aramine increases myocardial contractility in the normal dog heart (fig. 4*A*), in the heart with an anemic or a nonspecific type of failure (fig. 6*A*) and in the heart in which failure is due to coronary insufficiency (fig. 7). With a single intravenous dose of 0.05 mg. per kilogram the increase in myocardial contractility lasts for more than one hour (fig. 6*A*).

When graded doses were given it was seen that with small doses the effect was primarily on the myocardium and that further doses caused an increase in peripheral vascular resistance and tone. A differentiation of the effect of this drug on the myocardium and systemic vessels was also demonstrated by the time dissociation technic, using single intravenous doses, of 0.03 to 0.1 mg. per kilogram. There can be little doubt that both effects occur and are of significance. It is of additional interest that the myocardium did not require a greater blood flow per unit of work performed after the administration of this agent (fig. 6*B*), nor did it produce significant arrhythmias in the presence of severe myocardial hypoxia (fig. 7).

It was realized how approximate must be the attempt to simulate clinical coronary insufficiency experimentally. Nevertheless, in the experiment shown in figure 7, acute coronary insufficiency was induced as shown by the fall of arterial pressure, cardiac output and stroke work with a rising left atrial pressure when coronary flow was arbitrarily restricted.[6] It is of considerable interest that, with the coronary screw clamp still in place, the administration of Aramine was followed by an elevation of cardiac output, aortic pressure and coronary flow to or near control levels; and, as important, the left atrial pressure fell

below control levels after the drug arrived at the myocardium.

Somehow the view has become widespread that a "vasopressor" agent which elevates arterial pressure solely by its effect on peripheral vascular resistance has a peculiar virtue. "The aim of the use of vasopressor drugs in the treatment of shock following acute myocardial infarction is to increase the mean aortic pressure and thus reestablish an adequate coronary blood flow."[14] "The ideal pressor drug would elevate blood pressure, increase peripheral resistance, produce a proportionate increase of coronary flow, have minimal side effects, and would not decrease cardiac output or produce serious arrhythmias."[15] It is, of course, desirable to have an adequate coronary perfusion pressure and recent data from this laboratory attest to the importance of this factor in the myocardial failure of late hemorrhagic shock.[3] The data presented above, however, are not consonant with the view that this is the sole or most important single characteristic of an agent for the treatment of shock due to myocardial infarction. The lung edema that too frequently accompanies this syndrome must be influenced by the level of left atrial pressures when these are elevated. But more important, examination of the time-dissociation graph in figure 5 and the tracing in figure 7 shows that, when the sole effect is peripheral constriction, cardiac output is not augmented or even falls, and left atrial pressure rises further as it must for the ventricle to do the increased work.[5] A more desirable therapeutic goal, namely, an increased arterial pressure *and* cardiac output at lower atrial pressures is achieved only when the drug arrives at the myocardium and improves its function. The more favorable ventricular function curves obtained after Aramine make it apparent why this occurs.

The authors do not wish to indicate by the above that the cardiovascular effects of Aramine are unique to this particular sympathomimetic amine. Gazes, Goldberg and Darby,[16] using a strain gage attached to the right ventricle, showed that the latter contracted more forcefully after the administration of norepinephrine (Levophed). Simultaneous atrial pressures were not described so that it cannot be ascertained from their experiments whether or not the agent actually increased myocardial contractility or whether the ventricles were contracting more forcefully because of an increased filling pressure. Preliminary experiments in this laboratory, which included the simultaneous determination of filling pressures and ventricular work, indicate that norepinephrine does increase myocardial contractility. These data and the data on Aramine presented above support the views of Gazes, Goldberg and Darby who seriously question the premise that the therapeutic benefit resulting from the use of "vasopressor" agents derives solely from their peripheral vascular action.

Basically, coronary insufficiency depresses the ventricular function curve which leads to a descending spiral involving lowered output, lowered coronary perfusion pressure and higher atrial pressures.[6] The effect of certain of the aromatic amines is to reverse this spiral by producing a higher output, increased peripheral resistance, and higher coronary perfusion pressure at lower atrial pressures. It is clear that little can be achieved without enough residual functioning parenchyma to put to work. Ultimately, concern must be directed at those circumstances wherein temporary support may avert an acute disaster until the myocardium regains more adequate function.

Additional information on the hemodynamics of induced coronary insufficiency and the influence thereof on the ventricular function curves may be found in a previous publication.[6] The renal and cardiovascular effects of Aramine in normal man have recently been reviewed by Beyer.[1] A study of this agent in patients with hypotension resulting from myocardial infarction has been undertaken and will be published subsequently.

The above data have not been herein evaluated in terms of the effect of Aramine on coronary vascular tone. This stems from the authors' belief that coronary tone is controlled preponderantly by the work and oxygen requirements of the myocardium (fig. 6*B*). Figures 3 and 5 do show a decreased coronary

resistance following the administration of Aramine as do previous studies.[2, 3] Similarly, in figure 7, after Aramine, left coronary artery flow came back almost to its control level at similar aortic pressures, although the perfusion pressure in the vessel must have been substantially lower since the screw clamp was still in place. Myocardial work plays such a large role in controlling coronary tone that it is difficult to state whether or not Aramine is a *direct* coronary vasodilator. In any case its administration is followed by an increase in coronary flow both in the normal dog and one in which coronary stenosis, hypotension and a low cardiac output have been induced. Perhaps of greater importance is the fact that the drug increases the amount of work per unit of filling pressure without requiring more coronary flow per unit of ventricular work.

Summary and Conclusions

1. In the normal anesthetized dog Aramine produces a slight to moderate elevation of arterial pressure and a bradycardia. When the bradycardia is abolished either after vagotomy or during hemorrhagic hypotension Aramine produces marked elevations of arterial pressure.

2. The effects of the drug on cardiac output, coronary flow, atrial and arterial pressures and peripheral vascular resistance have been presented.

3. In small doses Aramine produces a striking improvement in the ventricular function curves of both the right and left ventricles (more stroke work at any given filling pressure). Subsequent doses do not further improve myocardial contractility but do increase peripheral vascular resistance and tone.

4. This bivalent effect on heart and periphery was also demonstrated by a time-dissociation technic.

5. The myocardium does not require a greater coronary flow per unit of work after the administration of Aramine.

6. Acute coronary insufficiency was induced by adjusting a clamp on the tube feeding the left main coronary artery. This produced a fall of arterial pressure, cardiac output and ventricular stroke work, and a rise of left atrial pressure. The subsequent intravenous injection of Aramine (with the screw clamp still in place) returned these values to or near their control levels.

7. The authors seriously question the premise that an agent for treating the hypotension of cardiogenic shock should achieve its effect solely or predominantly by producing peripheral vasoconstriction.

Sumario Español

1. En el perro normal anestesiado "Aramine" produce de una ligera a una moderada elevación en la presión arterial y una bradicardia. Cuando se abole la bradicardia o después de vagotomía o durante la hipotensión hemorrágica "Aramine" produce marcadas elevaciones de presión arterial.

2. Los efectos de la droga en la producción total cardíaca, circulación coronaria, presiones atriales y arteriales y resistencia periferal vascular han sido presentados.

3. En pequeñas dosis "Aramine" produce mejoría sorprendente en las curvas de función ventricular de ambos, ventrículo derecho e izquierdo (mayor trabajo por contracción a cualquier presión de henchimiento). Dosis subsiguientes no mejoran más la contracción del miocardio pero aumentan la resistencia perifero-vascular y el tono.

4. Este efecto bivalente en el corazón y periferia también se demostró por la técnica de disociación de tiempo.

5. El miocardio no requiere una circulación coronaria mayor por unidad de trabajo luego de la administración de "Aramine".

6. Insuficiencia coronaria aguda fué inducida ajustando una grampa al tubo de alimentación de la arteria coronaria principal izquierda. Esto produjo un decremento en presión arterial, producción cardíaca y trabajo por contracción ventricular y un incremento en presión atrial izquierda. La subsiguiente inyección intravenosa de "Aramine" (con la grampa tornillo aún en sitio) reintegró los valores a, o cerca de los niveles controles.

7. Los autores seriamente dudan la premisa de que un agente para el tratamiento del choque cardiogénico pueda producir su efecto solamente o predominantemente por la vasoconstricción periférica.

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Serum Lipid and Protein Fractions

IX. Comparisons of Ninety-six Patients with Vascular Disease and Sixty Normal Controls (with Additional Notes on Blood Donors)

By Irving Leinwand, M.D. and Dan H. Moore, Ph.D.

Ninety-six patients were observed at intervals for as long as three and one-half years in some cases. In most instances multiple determinations were made during this time using the electrophoretic pattern of the proteins before and after cold ether extraction (McFarlane method), to measure lipid transport. Hyperlipemia usually produced an increased in beta globulin. A varying decrease in albumin accompanied any increase in globulin. Phosphate and barbiturate buffers were used in this study. In setting up a control group, it was noted that the sera from professional blood donors contained relatively less albumin and more globulin than the sera of the nondonor group of hospital personnel.

FOR the past few decades, it has been common knowledge that in certain diseases the incidence of arteriosclerosis is much higher than in other diseases. About five years ago, a study of the lipid and protein fractions in these diseases was undertaken in an effort to determine if possible, some basis for this preferential incidence in these particular diseases.

Material and Methods

The groups of patients consisted of individuals with apparent occlusive vascular disease, in various stages of disability, as well as patients with assumed vascular disease without clinical evidence of occlusion. Included in the first category are 32 patients with arteriosclerosis obliterans, seven patients with myocardial infarction, and 28 patients with thromboangiitis. In the latter category are three patients with angina pectoris, 10 patients with hypertensive vascular disease, four patients with hypothyroidism, and 12 patients with primary essential xanthomatosis. These 96 patients were observed for varying periods of time up to three and one-half years. Sixty normal adults were used as controls.

The blood specimens were obtained in the morning after about 10 to 12 hours of fasting since this appeared to be an optimum time for a constant level of the lipids. Lipid estimations were chiefly concerned with lipid phosphorous and total cholesterol. In some patients the total lipids were determined. Fatty acid determinations were also made in most instances. During the first year of study, the electrophoretic analyses were done at a pH of 7.4 in a phosphate buffer, 0.02 M with respect to the sodium phosphate and 0.15 M with respect to sodium chloride.[1, 2] Subsequently, a barbiturate buffer was used at a pH of 8.6, 0.1 M with respect to sodium diethylbarbiturate and 0.02 M with respect to the diethylbarbituric acid.[3] These two buffers were used in order to permit a comparison of protein patterns with those in previously published reports of other investigators. Phosphate buffer produces a pattern which is easier to measure. The use of barbiturate buffer makes possible the separation of an additional component alpha 1, from the albumin fraction.

Patterns were secured before and after cold ether extraction by the McFarlane method[4] since this appeared to leave the protein structure comparatively undisturbed. Two volumes of serum were thoroughly mixed with one volume of ether and quickly frozen in a dry ice-alcohol bath. The samples were then allowed to thaw, whereupon the serum layer was carefully removed from underneath the ether layer with a syringe and long needle. The process was repeated four times on all samples, although most of the changes in the pattern took place after the first extraction.[5] As was pointed out by McFarland,[4] low temperature treatment of the ether-serum emulsion removes only part of the total lipids. Faber and Chargaff[6] have shown that most of the cholesterol is removed at the first extraction but that small quantities of phospholipids may continue to be removed even at the tenth or twelfth extraction. This has been confirmed in our own laboratory.[7] By measuring the patterns before and after cold ether

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TABLE 1.—*Electrophoretic Analysis of Serum from 43 Patients Using Phosphate Buffer at a pH of 7.4. Component Distribution Is Given in Per Cent of Pattern Area with the Standard Deviation, S.D. The Percentage Loss in Pattern Area after Cold Ether Extraction Is Given Underneath the Original Values. These Are Mean Figures of 132 Determinations*

Disease	Patients	Distribution of Electrophoretic Components							
		Albumin		Globulins					
				alpha		beta		gamma	
		%	S.D.	%	S.D.	%	S.D.	%	S.D.
Angina	2	59.2 −4.3	6.4	9.1 −24.3	0.5	20.9 −52.9	0.1	11.2 −4.1	5.2
Arteriosclerosis obliterans	15	58.0 −13.6	5.0	8.7 −22.7	2.0	17.2 −51.0	4.3	15.6 −27.3	4.1
Hypertensive vascular	3	58.6 −19.5	4.3	4.8 −23.5	2.3	17.9 −48.0	2.1	18.7 −41.1	4.8
Hypothyroid	1	58.8 −19.9	0.9	8.4 −46.3	2.5	18.7 −54.8	0.9	14.1 −50.5	4.6
Thromboangiitis obliterans	16	59.9 −13.7	4.6	8.0 −17.0	2.0	16.4 −46.8	2.1	15.9 −27.3	5.2
Primary essential xanthomatosis	6	54.7 −15.1	3.5	8.6 −34.7	1.6	20.8 −52.4	4.1	16.2 −29.5	4.4
Normal	12	61.4 −13.5	5.2	6.5 −21.4	0.3	15.6 −48.2	0.7	16.5 −31.5	3.3

extraction, a comparative study of lipid transport was possible. The possibility that cold ether extraction could modify the electrophoretic mobility of the components was investigated. There was no significant change. Lipids and cholesterol were determined on separate aliquots. When the phosphate buffer was used, the total lipids and fatty acids were determined by the method of Bloor,[8] total cholesterol by a modification[9] of the Sackett method,[10] and the lipid phosphorous after Whitehorn.[11] When barbiturate buffer was used, the fatty acids were determined according to the method of Bauer and Hirsch,[12] the cholesterol determinations according to Bloor,[13] and the lipid phosphorous after Fiske and Subbarow.[14] Occasionally there was not enough serum obtained for all of the determinations. In the group of patients studied with the barbiturate buffer, total lipids were not determined.

Serum was used throughout this study rather than plasma to avoid the fibrinogen peak. Calculations of the areas in the electrophoretic patterns were expressed as percent of the total area.

RESULTS

The figures in the tables are the mean figures of many determinations. It would be impossible to include all of them in any one report. More detailed information will appear in other reports.

Table 1. The analyses in this group of 43 patients studied with a phosphate buffer, showed variable decreases in albumin of minor degree except in primary essential xanthomatosis where there was a marked decrease. The alpha and beta globulins were uniformly elevated to some degree in all of these diseases. The only disease which showed even a slight elevation of the gamma globulin was hypertensive vascular disease. In regard to the lipid associated with these protein fractions, the loss after ether extraction by this method was fairly uniform except for the gamma globulin fraction. This uniformity of the means is, however, quite deceptive, since the individual determinations often showed considerable variation not only with each other in the same disease group, but in the same individual.

Table 2. The analyses in this group of 68

TABLE 2.—*Electrophoretic Analyses of Serum from 68 Patients Using Barbiturate Buffer at a pH of 8.6. Component Distribution Is Given in Per Cent of Pattern Area with the Standard Deviation (S.D.). The Percentage Loss in Pattern Area after Cold Ether Extraction Is Given Underneath the Original Values. These Are Mean Figures of 338 Determinations*

Disease	Patients	Distribution of Electrophoretic Components									
		Albumin		Globulins							
				Alpha 1		Alpha 2		Beta		Gamma	
		%	S.D.	%	S.D.	%	S.D.	%	S.D.	%	S.D.
Angina	2	53.7 −20.6	6.6	5.1 −22.0	0.5	10.7 −21.6	2.3	19.9 −68.6	4.2	10.2 −19.7	0.4
Arteriosclerosis obliterans	21	56.0 −13.4	3.7	4.9 −19.0	1.1	11.0 −20.5	2.6	16.0 −58.2	2.2	12.3 −27.7	1.9
Hypertensive vascular	11	54.2 −16.7	7.2	5.7 −19.6	1.1	9.7 −10.0	2.7	15.8 −58.0	3.0	14.1 −23.1	6.6
Hypothyroid	3	54.6 −8.9	4.5	5.5 −19.6	1.3	10.6 −15.0	1.3	16.3 −45.5	0.7	13.0 −10.8	4.9
Myocardial infarction	6	54.0 −14.5	7.8	5.9 −18.9	2.3	12.2 −26.4	4.8	17.0 −57.7	1.4	10.8 −20.7	2.0
Thromboangiitis obliterans	13	57.3 −12.7	3.9	5.3 −20.6	0.9	9.8 −26.9	2.4	15.7 −57.4	2.2	12.1 −34.3	1.0
Primary essential xanthomatosis	12	50.3 −9.6	4.4	5.0 −18.4	0.9	10.3 −12.3	0.9	22.0 −63.2	2.7	12.6 −17.1	2.5
Normal	41	61.0 −7.4	4.9	4.9 −5.4	0.5	8.9 −10.2	0.8	14.9 −55.1	2.4	12.0 −16.9	2.7

patients studied with barbiturate buffer, showed essentially the same trend. Again variable decreases in albumin were seen which was most marked in primary essential xanthomatosis. The alpha-$_1$ globulin remained fairly constant. The alpha-$_2$ and beta globulins were slightly increased in some groups and more markedly increased in others. The gamma globulin was slightly elevated in hypertensive vascular disease.

After ether extraction the difference in pattern area was calculated and expressed as the per cent change in area loss. This loss was greater in most of these diseases than it was in the normal controls, regardless of the type of buffer used. The percentages of the protein components are not comparable for these two buffers in regard to absolute figures except for the beta globulin. In spite of this the trend of the patterns is the same when compared to the normal controls for each buffer.

The variation of the lipoprotein pattern was previously reported by one of us.[15] A biologic swing was noted by Jones, Gofman, and their group[16] which has not been sufficiently studied or emphasized. In our studies, this viariation in the same individual was such as almost to nullify the value of any single determination. Multiple determinations in the same individual over some period of time is necessary in order to decrease the errors possible with single specimens of such variable components. This variability is noted in another report from our laboratory,[17] although it is indicated by the standard deviation given for each group in tables 1 and 2. It is quite possible that this variation is responsible for the recent conflicting reports of ultracentrifigul studies in these diseases. Although most of these studies in this present report were made in the fasting state, there is no difference in patterns obtained in the nonfast-

ing state as far as we could determine by these methods.[18] Therefore, these variations are probably not directly due to the immediate food intake.

Arteriosclerosis Obliterans. Table 3 shows the difference in protein pattern in 32 patients with the identical disease, arteriosclerosis obliterans, divided into two main groups by buffer and the absence or presence of hypercholesteremia. This table demonstrates the higher percentage of beta globulin in those patients with hyperlipemia and/or hypercholesterolemia than in those with normal levels regardless of the type of buffer used.

Thromboangiitis Obliterans. Table 4 gives the findings in 28 patients with thromboangiitis obliterans divided again into groups by buffer and the presence or absence of hypercholesteremia. There was practically no difference in the mean beta globulin of these patients regardless of the level of the lipids or the type of buffer used. The patients with hyperlipemia appeared to have a slightly higher alpha-$_2$ globulin and a slightly lower gamma globulin than those with normal levels. The mean determinations of the entire group showed a slight elevation of the beta globulin which was not really significant, so that the electrophoretic pattern as a whole appears much the same as the normal controls.

Myocardial Infarction. All of these patients showed an increase in alpha-$_2$ globulin and beta globulin with a decrease in albumin. The highest alpha-$_2$ globulins were seen in three patients who were in shock when the blood specimens were secured. One of these patients died in 12 hours, a second in 24 hours, and the third in several days. The elevation of the alpha-$_2$ globulin in shock has been described in the experimental animal by Moore [19] and by Lewis, Page, and Glasser.[20] The increase in this component in human shock has not to our knowledge been previously reported.

Angina. Patients with this complaint all showed hypercholesteremia with a reflected increase in the beta globulin and a decrease in the albumin. None of these patients had evidence of myocardial infarction.

Hypertensive Vascular Disease. None of the 10 patients examined had evidence of myocardial infarction. One female member of this group had had two episodes of cerebral vascular accidents. They had decreases in albumin with slight increases in beta and gamma globulin.

Hypothyroidism. These patients showed varying degrees of hypercholesteremia and variable increases in beta globulin. No characteristic pattern was noted. None of these patients had myxedema.

Primary Essential Xanthomatosis. Reported in this group are the four types described by Thannhauser,[21] xanthelasma, tendon xanthoma, xanthoma tuberosum, and the forme fruste. Analysis of the serum, which was clear, fulfilled the criteria as described. Eight of these patients were females. All of these patients were from families where there were

TABLE 3.—*Electrophoretic Analyses of Single Specimens of Serum from 32 Patients with Arteriosclerosis Obliterans. Component Distribution Is Given in Per Cent of Pattern Area*

Hyperlipemia	Buffer	Distribution of Electrophoretic Components				
		Albumin	Globulins			
			Alpha$_1$	Alpha$_2$	Beta	Gamma
Present	Phosphate,	57.0		7.9	17.9	16.6
Absent	pH 7.4	58.0		9.9	14.4	17.6
Present	Barbiturate,	56.5	4.4	9.4	17.4	12.2
Absent	pH 8.6	58.2	4.2	10.1	14.6	12.9

TABLE 4.—*Electrophoretic Analyses of Single Specimens of Serum from 28 Patients with Thromboangiitis Obliterans. Component Distribution Is Given in Per Cent of Pattern Area*

Hyperlipemia	Buffer	Distribution of Electrophoretic Components				
		Albumin	Globulins			
			Alpha$_1$	Alpha$_2$	Beta	Gamma
Present	Phosphate,	60.3		10.1	16.6	12.9
Absent	pH 7.4	59.5		6.9	16.5	17.1
Present	Barbiturate,	57.8	5.1	11.8	16.4	10.5
Absent	pH 8.6	54.8	5.1	9.6	15.8	13.6

TABLE 5.—*Electrophoretic Analyses of Serum from Personnel Used as Normal Controls and from Professional Donors of Two Blood Banks in New York City Hospitals Using Barbiturate Buffer at a pH of 8.6. Component Distribution Is Given in Per Cent of Pattern Area with the Standard Deviation (S.D.)*

Group	Number	Distribution of Electrophoretic Components									
		Albumin		Globulins							
				Alpha 1		Alpha 2		Beta		Gamma	
		%	S.D.	%	S.D.	%	S.D.	%	S.D.	%	S.D.
Normal	41	61.0	4.9	4.9	0.5	8.9	0.8	14.9	2.4	12.0	1.4
Donors (pooled)	20	57.9	1.7	5.3	0.7	11.5	1.0	14.1	0.8	11.2	2.0
Donors	10	55.4	2.1	5.4	0.7	12.1	0.7	14.1	0.8	13.0	1.1
Donors	9	53.3	3.6	6.5	1.1	9.7	2.1	16.8	2.9	13.6	3.3

histories of death from myocardial infarction of from one to three males in the immediate family. Two pairs of patients were related. Analysis of this group of patients showed a marked decrease in albumin and a marked increase in the beta globulin. Although the mean gamma globulin is within normal limits, at different intervals of time individual determinations frequently revealed a rise in the gamma globulin.

Normal Controls and Professional Blood Donors. The normal controls were made up of student nurses, technicians, physicians, and patients without obvious disease seen for routine examination. The professional donors were from two active blood banks in New York City hospitals. These included the usual share of derelicts. The pooled sera was from one of these blood banks and was divided into six samples each containing serum from three or four individuals. Table 5 gives a comparison of several samplings of this blood bank serum and the normal controls.

The analysis of the pooled sera is similar to that reported by Reiner, Fenichel, and Stern[22] for professional blood donors. They reported a difference in professional and nonprofessional blood donors. This difference is also apparent in our study. This difference is even more marked when the nonpooled sera of the other two groups is compared with the sera of our normal nonprofessional group. Protein patterns in many of these individual donors showed marked changes in the albumin-globulin ratio. Thymol turbidity tests and cephalin flocculation tests were often positive. In the group of nine donors, two patterns were within normal range. The other seven were so abnormal as to produce an abnormal mean in spite of two normal patterns. The mean figures of the 10 donors from another blood bank were little better. As one can see from the pooled samples, it is possible with an increase in the number of sera, to approach a more normal pattern. Thus pooled plasma with a sufficient number of normal donors might supply a solution with a normal albumin-globulin ratio but still contain abnormal albumins and globulins. Moreover, it is whole blood that is in common use since it should possess many advantages over plasma. Therefore, the use of blood which does not have a normal protein content is to be deplored. Not only is the attending physician or surgeon misled by a false sense of security, but the patient himself is endangered by inadequate therapy and the possibility of complications from the transfusion itself. Proper screening of donors would eliminate a large part of this risk. Several laboratory procedures could be used to eliminate blood which is found to be undesirable after it has slipped through the screening of the donors. Commercial laboratories using blood donors for various biologic products should also take heed of this problem since this situation is one which could produce some complicated medicolegal problems.

DISCUSSION

In the 96 patients with eight types of disease in which atherosclerosis is common, there is one common finding. This is the increase in the beta globulin. This is, however, not true for every individual with these diseases. While an examination of the mean determinations shows a trend toward an average pattern for

each group, it cannot be said that these patterns have any real diagnostic significance as a test for the presence or absence of atherosclerosis. There was no correlation between the severity of the lesions observed clinically, and the degree of increase in the beta globulin.

The groups of patients studied using the phosphate buffer at a pH of 7.4 showed a higher gamma globulin than did the groups studied with the barbiturate buffer at a pH of 8.6. This applied to the normal subjects too. This is probably due to the inclusion of an epsilon boundary in the gamma globulin of the phosphate buffer. Since the albumin plus the alpha-$_1$ of the barbiturate buffer should roughly equal the albumin of the phosphate buffer, the correlation of the percentages of these fractions for the two buffers is poor. These are technical considerations which will be discussed at greater length elsewhere. It does however emphasize the importance of the buffer and pH in comparing data on electrophoresis.

In considering these disease groups further, those patients with arteriosclerosis obliterans showed a good correlation between hyperlipemia and an increase in beta globulin. However there was a poor correlation between hyperlipemia and this disease, since 50 per cent of these patients had neither a hyperlipemia or hypercholesteremia.

In thromboangiitis obliterans, the slight increase in beta globulin in the absence of hypercholesteremia is unexpected. Since this disease is basically characterized by an inflammatory lesion, one would have expected an increase in the gamma globulin, since this fraction is said to contain the antibodies. There was, however, no increase in this fraction in the group of patients studied. An increase in beta globulin without an increase in serum lipids is also seen in pulmonary tuberculosis[23] and occassionally in sarcoidosis. The significance of this finding is not clear. Some investigators believe that this increase is an indication of healing.[24] The possibility that the beta globulin contains antibodies must be considered.

In primary essential xanthomatosis, not only is the albumin fraction decreased, but the amount of associated lipid lost after ether extraction is practically the same percentage loss as normal. Therefore, the amount of lipid associated with the albumin fraction is decreased in spite of the great increase in serum lipids. The small amount of lipid associated with the albumin fraction in primary biliary cirrhosis in the presence of greatly increased serum lipids has been noted by Kunkel and Slater.[25]

Conclusions

1. In the disease groups presented, the most significant decrease in the albumin fraction measured by electrophoresis was in primary essential xanthomatosis.

2. The alpha$_1$ globulin remained practically normal.

3. The alpha$_2$ globulin was slightly increased in all of these diseases to about the same degree except in those patients in shock due to myocardial infarction in whom it was markedly increased.

4. The beta globulin was increased to some degree in all of these diseases and was increased most in primary essential xanthomatosis.

5. The gamma globulin was within normal limits except in hypertensive vascular disease where it was slightly increased.

6. In arteriosclerosis obliterans, the beta globulin was usually within normal limits in the absence of hyperlipemia or hypercholesteremia. About 50 per cent of the patients with this disease observed in this study had normal serum lipid levels.

7. In thromboangiitis obliterans, the slight increase in the beta globulin fraction had no relation to the level of the serum lipids.

8. The professional donors had a lower albumin fraction and a higher globulin content than the nonprofessional donors. Many professional donors had a reversal of the albumin-globulin ratio.

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Sumario Español

1. En el grupo de enfermedades presentado, el decremento mas significativo en la fracción

de albumina medida por electroforesis fué en xantomatosis esencial primaria.

2. La globulina alpha$_1$ permaneció practicamente normal.

3. La globulina alpha$_2$ aumentó ligeramente en todas estas enfermedades más o menos el mismo grado excepto en aquellos pacientes en choque debido a infartos del miocardio en los cuales hubo un aumento marcado.

4. La globulina beta aumentó en algun grado en todas estas enfermedades y aumentó en grado mayor en la xantomatosis esencial primaria.

5. La globulina gama se encontró entre los límites normales excepto en la enfermedad hipertenso vascular donde se encontró ligeramente aumentada.

6. En la arterioesclerosis obliterante, la globulina beta se encontró usualmente entre los límites normales en la ausencia de hiperlipemia o hipercolesterolemia. Aproximadamente 50 por ciento de los pacientes con esta enfermedad observados en este estudio tuvieron niveles de lípido del suero normales.

7. En la tromboangiítis obliterante, el pequeño incremento en la fracción de globulinas beta no tuvo relación alguna al nivel de lípidos del suero.

8. Los donantes profesionales tuvieron una fracción de albúmina baja y un contenido mas alto de globulina que los donantes no profesionales. Muchos de los donantes profesionales tuvieron una inversión de la relación de albúmina-globulina.

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A Direct Experimental Study of Three Systems of Spatial Vectorcardiography

By Ernest Frank, Ph.D.

Three commonly used systems of vectorcardiography are compared on an absolute and direct quantitative basis in terms of equations, geometric interpretations, scalar leads and vectorcardiograms, using experimental results obtained on an accurate, three-dimensional homogeneous torso model of the human subject with a dipole fixed in position in the center of the heart. It is concluded that the accuracy of the three systems, as presently used, is unsatisfactory and that further consideration of the systems of Duchosal and Grishman is questionable because of excessive intrinsic errors. Certain chance properties of the Wilson tetrahedron enable standardization modifications which lead to fairly accurate results for some dipole positions, and this system also possesses other features which appear to be desirable. The applicability of the results and conclusions to the human subject depends upon the degree to which the human heart may be represented by a fixed-position dipole and the degree to which human body electrical inhomogeneities influence body surface potentials.

RECOGNITION that the electrical forces in the heart are three-dimensional in nature has precipitated an international, active quest for accurate means of recording their spatial aspects. A variety of electrode arrangements on the body surface of the human subject are presently being utilized by many electrocardiographers.[1-6] Most of these systems of vectorcardiography are founded upon the assumptions that the human torso is a substantially homogeneous volume conductor and that the heart forces may be represented by a single fixed-position, time-varying current dipole. The degree to which these assumptions are applicable to the human subject has not been firmly established. Additional assumptions are usually made by the advocates of various specific systems concerning the geometry of the body and the position of the dipole. However, it has been shown in this laboratory by exhaustive studies on human torso models that the shape of the human torso and the position of the equivalent heart dipole are important factors which introduce large errors in currently employed methods of vectorcardiography, even granting that the torso medium is homogeneous and that the heart forces may be consolidated into a single fixed-position dipole.

It is the purpose of this paper to extract from the tremendous amount of data obtained with male and female homogeneous torso models, moulded accurately to the human subject, representative findings which pertain to a few of the commonly used systems of spatial vectorcardiography. It is hoped that the shortcomings of all of these systems will be recognized by workers in this field so that they may be encouraged to follow more fruitful lines of investigation.

Systems of Vectorcardiography

If the assumption of a fixed-position dipole representation of the human heart is adopted, this is tantamount to assuming that there is essentially only a single entity to be determined on an individual human subject; namely, the three-dimensional variations of the dipole moment. This single entity then represents the total and complete information which is sought from body surface measurements.*

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* Precordial electrodes might give additional information if the dipole approximation becomes

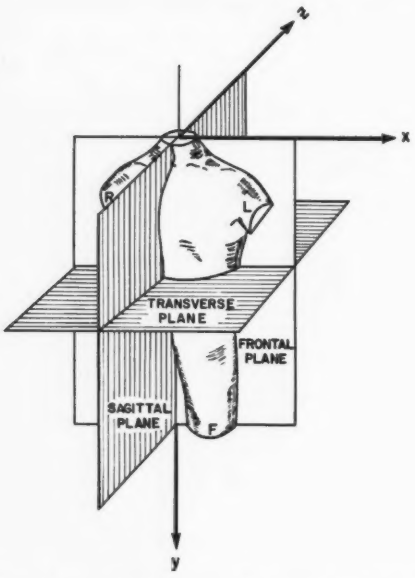

FIG. 1. A rectangular coordinate system defining three planes commonly used in vectorcardiography is illustrated. The nomenclature for these planes, and for the directions and letter designations of the rectangular axes has not been standardized officially.

The spatial dipole variations can be decomposed into three parts, for convenience in recording and study, by considering the projections on three rectangular axes, shown in figure 1, from which the spatial variations may be synthesized by considering various projections of the component variations. From a mathematical point of view, the single entity may be symbolized by the vector **p**,* the dipole moment which is a function of time. This heart dipole can be expressed in terms of its rectangular components as $\mathbf{p} = \mathbf{i}p_x + \mathbf{j}p_y + \mathbf{k}p_z$ where p_x, p_y and p_z are the components of the dipole and **i**, **j** and **k** are standard unit vectors of rectangular coordinates.[8] Thus, the problem of vectorcardiography, granting the dipole assumption, is to determine p_x, p_y and p_z simultaneously as functions of time. This has been the objective of various electrocardiographers doing research in this field.

Any three independent potential differences measured on the body surface can, in principle, lead to a determination of p_x, p_y and p_z, and the results obtained from any desired electrode arrangements should all agree,[9] provided the data are properly analyzed on a sound basis. From this standpoint it may be seen that the choice of electrode placement is really a practical one including such factors as reproducibility of electrode position, influence of dipole position at the electrode sites selected, and influence of body build. The results obtained for the three systems to be described, each of which employs different electrode positions, are not in agreement because of the inapplicability of the assumptions which are made concerning the relationship between the electrode potentials and the heart dipole; that is, the effects of dipole position and torso shape are not taken into account properly.

Duchosal-Sulzer System. The electrode arrangement advocated by Duchosal and Sulzer is illustrated in figure 2. The details regarding exact placement of electrodes n, o, p, q may be found elsewhere.[1] In this system it is assumed that the potential difference between p and o is proportional only to the x component of the dipole, p_x; that the potential difference between o and n is proportional only to the y component, p_y; and that the potential difference between o and q is proportional only to the z component, p_z. Moreover, it is assumed that the constant of proportionality is the same for each electrode pair. These ideas may be expressed compactly in terms of the following three equations, using the xyz coordinate system of figure 1.

$$V_p - V_o = cp_x, \qquad V_o - V_n = cp_y, \qquad V_o - V_q = cp_z \tag{1}$$

where V_n, V_o, V_p and V_q are the potentials of the electrodes with respect to the dipole midpotential and c is a constant of proportionality.

Grishman-Scherlis System. A modification of the Duchosal-Sulzer electrode arrangement has been advocated by Grishman and Scherlis, as illustrated in figure 2, but the assumptions

significantly inaccurate when electrodes are located close to the heart. The magnitude of this "proximity effect" has not yet been firmly established, but it is probably small.[7]

* Throughout this paper, vectors are indicated by boldface type.

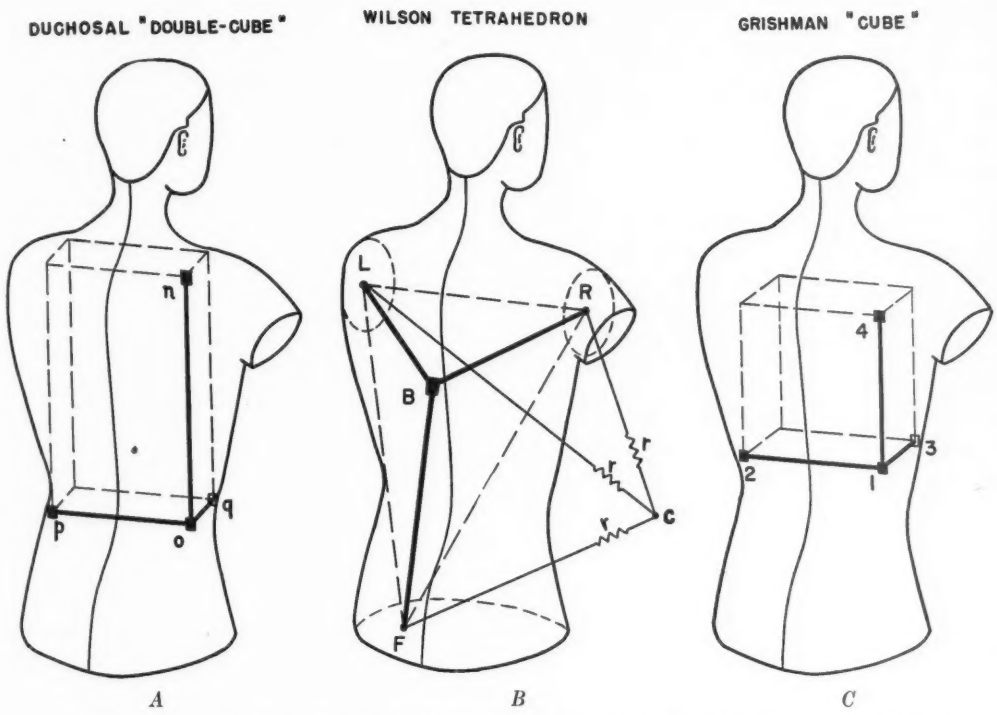

FIG. 2. Schematic illustration of the electrode arrangements employed in three commonly used systems of vectorcardiography. Letter and number identifications for the electrodes as originally presented are retained. The solid squares indicate electrodes placed on the back of the subject. The standard limb electrodes are indicated by R, L and F. A central terminal C is connected through equal resistors, r, to R, L and F.

are retained concerning the equal proportionality between the potential differences and the dipole component to which the line joining the physical electrodes is parallel. A description of the exact electrode placement may be found elsewhere.[2] The equations assumed to be applicable to this system are

$$V_2 - V_1 = kp_x, \qquad V_1 - V_4 = kp_y, \qquad V_1 - V_3 = kp_z \tag{2}$$

where V_1, V_2, V_3 and V_4 are the electrode potentials with respect to the dipole mid-potential, and k is a constant of proportionality, assumed to be the same for each electrode pair.

The treatment of the potential differences in this manner in both the Duchosal and Grishman systems is based upon such considerations as the directions of the anatomic lines joining the electrodes, the anatomic angles subtended by the electrodes from the heart center, and the anatomic distances from the electrodes to the heart center. However, it will be shown that this basis is not accurate for these electrode arrangements. Moreover, it has been shown elsewhere[10] that anatomic distances and angles are generally very distorted as far as electrical effects are concerned for practically all points on the surface of the torso.

Wilson Tetrahedron System. The electrode arrangement advocated by Wilson and associates[3] is shown in figure 2. Three electrodes R, L and F are the standard limb electrodes and electrode B is located on the back approximately 1.0 inch to the left of the seventh dorsal vertebra. The treatment of the potential differences in this system is based rigidly upon a homogeneous conducting sphere with a centric dipole, which is about as arbitrary

as the anatomic basis discussed above. Two types of theoretical tetrahedrons inscribed in the sphere have been advocated, the equilateral tetrahedron and the isosceles tetrahedron, even though the electrode placement on the human subject is the same in both cases. In the equilateral tetrahedron the dipole at the center of the sphere is equidistant from each of the four points R, L, F and B on the surface of the sphere; the dipole is at the center of the tetrahedron and the frontal-plane triangle is located in front of the dipole parallel to the frontal plane. In the isosceles tetrahedron the centric dipole lies in the plane of the frontal-plane triangle and again the distances from R, L, F and B to the dipole are equal. The mathematical equations obtained depend upon which theoretic model is used; the equilateral tetrahedron will be discussed here since it gives the best agreement in scalar-lead wave shape with results in torso models. For the equilateral tetrahedron it has been shown[3] that the following unipolar voltages are produced by a centric dipole in the homogeneous conducting sphere:

$$\begin{aligned} V_R &= K(-\sqrt{6}\,p_x - \sqrt{2}\,p_y - p_z) \\ V_L &= K(\sqrt{6}\,p_x - \sqrt{2}\,p_y - p_z) \\ V_F &= K(0p_x + 2\sqrt{2}\,p_y - p_z) \\ V_B &= K(0p_x + 0p_y + 3p_x) \end{aligned} \qquad (3)$$

where V_R, V_L, V_F and V_B are the potentials of the electrodes with respect to the dipole mid-potential, arbitrarily assigned the value zero, and K is a constant of proportionality.

A study of these four equations indicates that potential differences proportional to only one component of the dipole may be obtained theoretically by the use of a central terminal connected from R, L and F through three equal resistors, r, as shown in figure 2.* This corresponds to the "Equilateral Tetrahedron, Case II," analyzed by Cronvich.[11] It is interesting to note that the potential of this central terminal is not theoretically zero, being given by

$$V_C = \tfrac{1}{3}(V_R + V_L + V_F) = -Kp_z \qquad (4)$$

* A central terminal in which all four electrodes are joined through four equal resistors is sometimes used. In the idealized schema, this junction is theoretically at the same potential as the dipole mid-potential.[3]

assuming the resistors, r, are very large in comparison with the resistance behind the electrodes. It may be seen from equations 3 and 4 that the following potential differences are obtained for theoretically determining the three dipole components:

$$\begin{aligned} V_L - V_R &= 2K\sqrt{6}\,p_x, \\ V_F - V_C &= 2K\sqrt{2}\,p_y, \\ V_B - V_C &= 4Kp_z \end{aligned} \qquad (5)$$

In contradistinction to the other systems discussed, it will be noted that these potential differences do not have equal proportionality constants.

Treatment of the potential differences in this manner, based on a theoretical model of a centric dipole in a homogeneous conducting sphere, is considerably erroneous[12] since the human torso is not spherical in shape and the heart dipole is not centrically located. It will be shown that the tetrahedron which applies to a torso with an eccentric dipole departs drastically from that inscribed in the sphere.

Experimental Method

By the use of a homogeneous conducting torso with an immersed fixed-position dipole, it has been possible to obtain detailed information enabling the dipole variations p_x, p_y and p_z to be calculated precisely from any designated electrode positions on the torso surface. It has been found convenient to summarize the results in the form of an image surface[9, 10] which, in addition to enabling any system of vectorcardiography to be analyzed, gives insight into many aspects of other problems faced in electrocardiography. With these data it can be shown that exactly the same dipole variations are deduced regardless of the electrode positions used. However, if the assumptions made by the advocates of various systems are applied to their electrode positions, results are obtained which do not agree with those which were determined by direct experiment, and, furthermore, each system entails errors of different kind and degree. These errors are superimposed upon those which are already inherent in the assumptions concerning the dipole representation of the heart and the homogeneity of the conducting medium.

The experimental apparatus and method is described in detail elsewhere.[12-15] For this particular study, the finite dipole was fixed in position within the homogeneous conducting torso in the center of the region occupied in life by the ventricular mass during very deep inspiration. True unipolar voltages were determined in both male and female torso

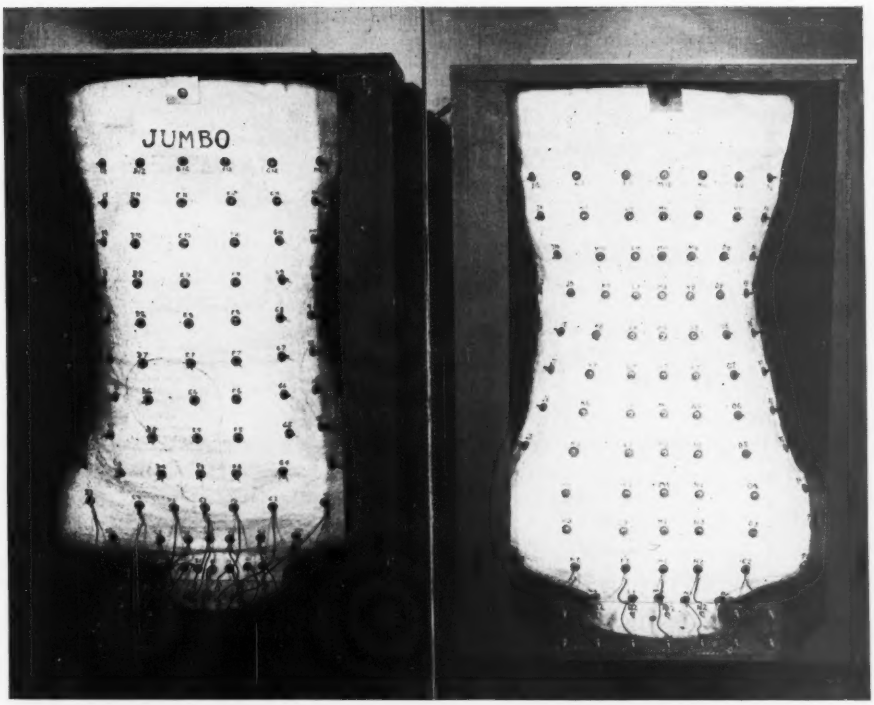

FIG. 3. Front and rear views of the life-size male torso model used experimentally. This model was moulded to the human subject using a wax-impregnated cloth. The inside was made waterproof with a thin lining of latex and the outside was bound with plaster bandage to obtain rigidity. Watertight electrodes pierce the torso walls and make contact with the liquid inside. The model is inverted to enable more flexibility in positioning the dipole (supported on the end of an insulating rod) than would be possible through the neck.

models at approximately 200 boundary electrode positions on each. From these data, which have been analyzed comprehensively and expressed in the form of image surfaces,[10] the voltages pertaining to the 12 electrode positions shown in figure 2 were singled out for presentation here for a male torso of average build (chest: 40 inches, hips: 38 inches, waist: 32½ inches). Photographs of this torso model are shown in figure 3. The relationship between the unipolar voltages at the points n, o, p, q 1, 2, 3, 4, R, L, F, B and the dipole immersed within the torso could be determined directly since the dipole was located in a known and accurately-prescribed manner. The data obtained are accurate to approximately 5 per cent.

RESULTS

The complete results may be summarized succinctly in the form of equations which relate the true unipolar voltage of the electrode in question to the three components of the heart dipole. These equations are given in table 1, where the numerical coefficients are in the same relative units. The equations in table 1 contain the complete results of this study. While they possess the advantages of completeness and brevity, it is recognized that their implications may not be fully appreciated without a detailed discussion. Therefore, they will be interpreted in a variety of ways in the section which follows.

INTERPRETATION OF RESULTS

Bipolar Equations. The bipolar equations which pertain to each of the three systems may be obtained by subtracting appropriate unipolar voltages. The central terminal voltage may be computed from table 1 for the torso model as follows:

$$V_C = \frac{1}{3}(V_R + V_L + V_F) = -16p_x - 17p_y + 26p_z \quad (6)$$

TABLE 1.—*Unipolar Equations*

Duchosal	Grishman	Wilson
$V_n = -39p_x - 65p_y + 34p_z$	$V_1 = -50p_x + 62p_y + 24p_z$	$V_R = -51p_x - 57p_y + 27p_z$
$V_o = -32p_x + 83p_y + 14p_z$	$V_2 = 16p_x + 82p_y + 46p_z$	$V_L = 25p_x - 84p_y + 41p_z$
$V_p = -11p_x + 90p_y + 19p_z$	$V_3 = -51p_x + 75p_y - 7p_z$	$V_F = -21p_x + 91p_y + 11p_z$
$V_q = -34p_x + 85p_y + 3p_z$	$V_4 = -44p_x - 60p_y + 35p_z$	$V_B = -16p_x - 13p_y + 90p_z$

TABLE 2.—*Bipolar Equations*

Duchosal	Grishman	Wilson
$V_p - V_o = 21p_x + 7p_y + 5p_z$	$V_2 - V_1 = 66p_x + 20p_y + 22p_z$	$V_L - V_R = 76p_x - 27p_y + 14p_z$
$V_o - V_n = 7p_x + 148p_y - 20p_z$	$V_1 - V_4 = -6p_x + 122p_y - 11p_z$	$V_F - V_C = -5p_x + 108p_y - 15p_z$
$V_o - V_q = 2p_x - 2p_y + 11p_z$	$V_1 - V_3 = p_x - 13p_y + 31p_z$	$V_B - V_C = 0p_x + 4p_y + 64p_z$

TABLE 3.—*Per Cent Disturbing Coefficients*

Heart-Dipole Component Desired	Duchosal			Grishman			Wilson		
	p_x	p_y	p_z	p_x	p_y	p_z	p_x	p_y	p_z
p_x		33	24		30	33		−36	18
p_y	5		−14	−5		−9	−5		−14
p_z	18	−18		3	−42		0	6	

Carrying out the necessary subtractions, the bipolar results given in table 2 are obtained from table 1. A comparison of the equations in table 2 with those claimed to apply for the various systems, as shown in equations 1, 2 and 5, reveal glaring discrepancies which become apparent at once. None of the bipolar voltages is proportional to only one component of the heart dipole, although in all cases the single components which are assumed in equations 1, 2 and 5 do have coefficients which are larger than the disturbing (undesired) coefficients. The bipolar equations which pertain to the Duchosal and Grishman systems have far from equal proportionality factors c and k as assumed in equations 1 and 2, and the relative proportionality factors theoretically called for in equation 5 for the Wilson system do not agree with those for the torso model. A quantitative measure of the proportionality factors is given later in figure 6 in which the relative amplitude factors required for each bipolar lead to give a best fit for an assigned dipole variation has been noted. The central terminal voltage for the torso model, given in equation 6, can also be seen to be far from agreement with the theoretical result of equation 4.

An approximate measure of the faithfulness of recording the correct *shape* of a given dipole component for each lead (regardless of the relative amplitude) may be obtained by comparing the disturbing coefficients with the coefficient of the dipole component which is presumed to be measured in a given lead. For example, $V_p - V_o$ is presumably proportional to p_x only according to equation 1 but, from table 2, it can be seen that the coefficients of p_y and p_z are 7 and 5, respectively, which correspond to 33 per cent and 24 per cent of the coefficient of p_x, which is 21. Following this line of reasoning, the results shown in table 3 are obtained. These per cent disturbing coefficients do not constitute an exact measure of the shape distortion of a given lead, since p_x, p_y and p_z are each different functions of time. The disturbing terms may tend to cancel or reenforce one another, depending upon the instantaneous magnitude and polarity of p_x, p_y and p_z. However, these percentages are usually indicative of the shape errors. For instance, in figure 6, which shows specific typical functions for p_x, p_y and p_z, the reasonably good shape agreement for all three systems in the case of p_y could be expected from the fact that the per cent disturbing coefficients are all relatively small (5 to 14 per cent). Also, in the case of p_z the good agreement in shape for the Wilson and Duchosal systems and the relatively poor agreement in shape for the Grishman system is indicated by the per cent disturbing coefficients of table 3. In the case of p_x, an example is provided which shows that the signs of the disturbing co-

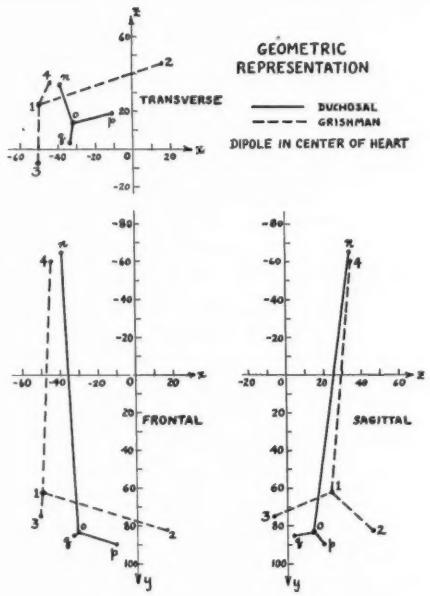

FIG. 4. Geometric representation of the electrode positions of Duchosal and Grishman in image space for a homogeneous torso with an immersed dipole. The heart dipole is located at the origin of the coordinate system. The potential difference between any pair of electrodes is obtained by projecting the heart dipole onto the vector joining the corresponding points in image space, and multiplying by the length of this vector. It may be seen in both qualitative and quantitative terms that these electrodes depart considerably from their anatomic positions.

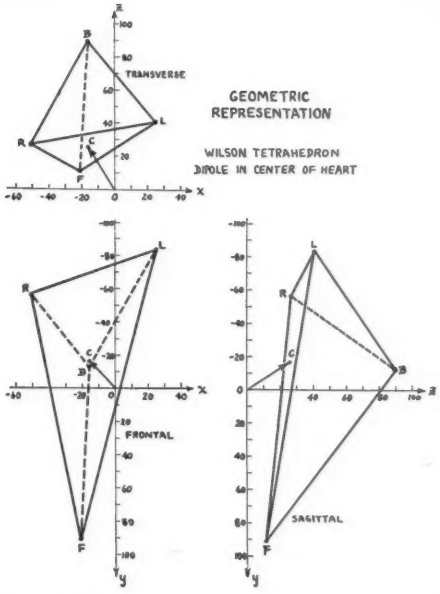

FIG. 5. Geometric representation of the Wilson tetrahedron in image space for a homogeneous torso with an immersed dipole. The same vector projection rule described in figure 4 is applicable. The Wilson central-terminal vector is directed from the dipole position O to the median point C of the limb-lead triangle R, L, F. It may be seen that these electrodes do not form an equilateral tetrahedron and that the heart dipole is far from the center of the tetrahedron.

efficients must also be considered, for the Wilson system yields a faithful p_x shape despite the existence of sizable disturbing coefficients. The disturbing terms tend to cancel almost completely in this case for the dipole functions illustrated in figure 6.

Geometric Interpretation. It has been shown elsewhere[9] that the unipolar equations given in table 1 may be expressed as the vector dot product of the heart dipole vector **p** with a vector **c** whose components are equal to the coefficients. For example, the unipolar voltage at electrode n may be written as

$$V_n = \mathbf{c}_n \cdot \mathbf{p} = (-39\mathbf{i} - 65\mathbf{j} + 34\mathbf{k}) \cdot (\mathbf{i}p_x + \mathbf{j}p_y + \mathbf{k}p_z) \quad (7)$$

The purpose of expressing the equations in this form is to enable a geometric interpretation. V_n may be looked upon as arising from the projection of **p** onto $\mathbf{c}_n$, multiplied by the length of $\mathbf{c}_n$. The constant vectors **c** for each of the unipolar voltages in table 1 can be constructed from a common origin and the tips of the vectors are the image points which correspond to the physical points on the torso. The 12 electrode image points for the systems under study here are shown in figures 4 and 5, where vector projection is valid, and are seen to depart drastically from the points in physical space on the torso surface. This means that the use of vector projection in physical space leads to large errors. The vectors joining the points in image space can be used to obtain the bipolar voltages by projecting **p** onto them and multiplying by their length. The basis for this vector projection scheme has been discussed in detail elsewhere.[9]

In terms of the geometric representation in figure 4, the defects of the Duchosal and Grishman systems may be seen in graphic terms. The

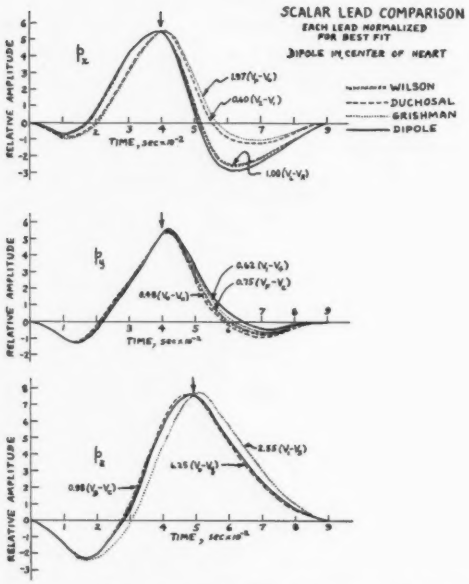

FIG. 6. Shape comparison of the potential differences produced on the torso by a fixed-position, time-varying heart dipole for each of the three systems for the QRS complex. The potential difference of each pair of leads has been multiplied by the factor shown in order to give the most favorable comparison in shape with p_x, p_y and p_z, indicated by the solid lines. The vertical arrows indicate the points at which the curves were fitted. The degree of shape agreement can be correlated with the data of table 3. This comparison is based solely on the scalar lead shape and disregards completely the amplitude defects of the systems which are very large, as shown in figure 7.

advocates of these systems claim in effect that the vectors in image space joining o, p and 1, 2 are parallel to the x axis; that the vectors joining o, n and 1, 4 are parallel to the y axis; and that the vectors joining o, q and 1, 3 are parallel to the z axis. That is, the points o, p and 1, 2 are presumed to coincide in the sagittal view; the points o, n and 1, 4 are presumed to coincide in the transverse view; and the points o, q and 1, 3 are presumed to coincide in the frontal view. Moreover, it is assumed that the lengths of all of these vectors are equal. In addition, it is assumed that the dipole, which is located at the origin of the coordinate system of figure 4, is equidistant from the four points of each system. It is clearly evident that these properties are not applicable to a homogeneous torso with a dipole in the heart center. The reader may assess for himself the magnitude of the errors implied by the diagram of figure 4 which has quantitative significance.

The "equilateral" tetrahedron of Wilson is shown as it appears in image space in figure 5. It is clear that the tetrahedron is not equilateral. Moreover, the heart dipole is located considerably in front of the limb-lead triangle rather than at the center of the tetrahedron as supposed in the spherical model. Further, the vector joining R and L is not parallel to the x axis (R and L do not coincide in the sagittal view), the vectors from the heart dipole (point O) to F is not parallel to the y axis and the vector from O to B is not parallel to the z axis.

By a fortuitous combination of effects, however, the Wilson system is not subject to errors as great as the Duchosal and Grishman systems, despite the glaring discrepancy between the tetrahedron in image space and the one inscribed in the idealized sphere.* It will be noted in figure 5 that the tip of the central-terminal vector,[9] drawn from the dipole (at the origin) to the median point of the limb-lead triangle, is nearly coincident with B in the frontal view, indicating that the vector between B and C is very nearly parallel to the z-axis and, therefore, that the potential difference $V_B - V_C$ will be very nearly proportional to p_z. This has also been indicated in table 3. Furthermore, the location of C with respect to point F in the transverse view shows that the vector joining C and F is more nearly parallel to the y axis than the vector through F and O, the true zero reference potential. Thus, the imperfection of the central terminal again tends to improve matters. In addition, while the vector from R to L is far from parallel to the x axis, it is so oriented in space (for this particular dipole position) that the contributions of the y and z components of the dipole tend to oppose one another. This may also be seen from the equation $V_L - V_R$ in table 2. The p_x leads of the other two systems do not possess this lucky property. As a result of these chance condi-

* The image surface of a homogeneous conducting sphere with a centric dipole is undistorted as compared with the physical sphere.[9]

tions, the tetrahedron, though departing drastically from the theoretical assumptions of Wilson, has certain potentialities which will be discussed in detail later.

QRS Complex Illustration. As a final method of interpreting the results of the torso-model studies, the scalar lead voltages and vectorcardiograms produced by a specific three-dimensional dipole variation may be compared, as they would be recorded by each system.[18] For this purpose the dipole is assigned variations which are believed to be applicable for a normal subject during the QRS complex, although the results are not critically dependent upon the particular choice of dipole variations. The same considerations apply for the P and T waves. The dipole functions p_x, p_y and p_z which have been selected for illustrative purposes are shown by the solid lines in figure 6 and the three projections of the dipole loops are given by the solid lines of figure 7.

(a) Scalar lead comparison. A comparison between the calculated bipolar lead voltages produced on the torso by the variable-moment, fixed-position dipole and the corresponding dipole component is given in figure 6. The relative amplitudes in each case have been adjusted for the best fit; the vertical arrows indicate the points at which the scalar leads of the various systems were forced to agree with the instantaneous amplitude of the dipole component. In order to accomplish this normalization, the standardization factors shown on figure 6 were used. These factors give a measure of the amplitude error involved in each system when the advocated standardization factors are employed. It may be seen that all three systems give fair agreement in shape with p_y, but that only the Wilson system gives acceptable agreement in shape in the case of p_x. In the case of p_z, Grishman's system can be seen to be significantly inferior to either of the other two systems. The cause for the disagreement in shape can be seen from tables 2 and 3 where the scalar leads produced by each system are seen to be molested by dipole components other than those presumed to be reflected in a particular lead.

(b) Vectorcardiograms. A more exacting comparison of the fidelity of each system may

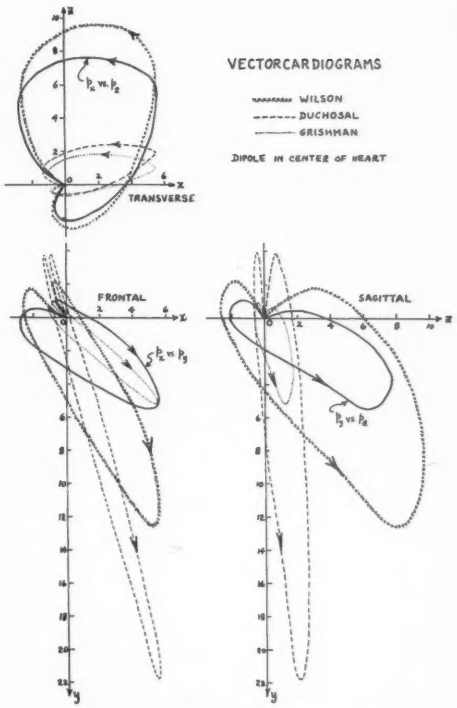

FIG. 7. Vectorcardiograms obtained in a homogeneous torso with a fixed-position, time-varying dipole are compared for each of the three systems using the methods proposed by their advocates. In each system the relative amplitudes have been adjusted to give agreement with p_z in peak amplitude; i.e., the relative factors shown for p_z in figure 6 have been used for all three leads of a given system. It is readily seen that none of these systems gives acceptable agreement with the heart dipole variations, shown by the solid curves.

be made in terms of the vectorcardiograms shown in figure 7 which would be recorded by using the standardization factors called for by the advocates of each system rather than those which are deliberately selected to make amplitudes agree based upon the torso behavior, as was done in figure 6. These vectorcardiograms are those which are obtained on the torso model applying equations 1, 2 and 5; that is, $V_p - V_o$, $V_o - V_n$, $V_o - V_q$ are recorded at equal amplification; $V_2 - V_1$, $V_1 - V_4$, $V_1 - V_3$ are recorded at equal amplification; $V_F - V_C$ is recorded at $\sqrt{3}$ times the amplification of $V_L - V_R$, and $V_B - V_C$ is recorded at $\sqrt{3/2}$

times the amplification of $V_L - V_R$. In all cases the relative amplitudes of each system have been adjusted to agree with p_z; i.e., if the amplification used for $V_L - V_R$ is taken as unity, then the amplification for the Duchosal p_x lead, $V_p - V_o$, is 1.97 and that of the Grishman p_x lead, $V_2 - V_1$, is 0.60.

It can be seen that the Duchosal system tends to elongate the loop enormously in the head-to-foot direction, and to contract drastically the chest-to-back component. The system of Grishman gives relatively close agreement (3 per cent) in the relative amplitudes of the p_z and p_y components, but the shape distortion of p_x, shown in figure 6, causes the frontal-plane loop to depart from the heart-dipole loop shape. The Grishman system also gives a contracted view of the chest-to-back component of the dipole. The Wilson system, while giving fair to good agreement in all of the scalar-lead wave shapes for this dipole position, does not reproduce the dipole vector loops faithfully, largely because the standardization factors called for by the spherical model are not suitable. The standardization factor for $V_F - V_C$ is too large by a factor of about $\sqrt{3}/0.75 = 2.3$, and that for $V_B - V_C$ is also too large by a factor of about $\sqrt{3/2}/0.98 = 1.25$. The effects of reducing the standardization factors are presented in the discussion.

Discussion

A detailed description of the results obtained with a homogeneous torso model of the human subject with a dipole immersed in the center of the heart has been given and compared with results that are obtained with three commonly used systems of vectorcardiography. None of these systems, when treated in accordance with the assumptions of their advocates, gives a faithful record of the true dipole variations. This conclusion is based upon direct experimental measurements. The same conclusion applies for a female torso, and for a wide variety of positions of the dipole within the heart volume. Thus, granting the assumptions of a fixed-dipole representation of the human heart and of a homogeneous conducting torso, it is concluded that these systems as presently used are not satisfactory.

Not all of the systems yield the same distortion, however. From the standpoint of reproduction of scalar-lead shape only, disregarding the relative amplitudes of each lead, they may be rated in the following order of descending merit: (1) Wilson, (2) Duchosal, (3) Grishman. An approximate quantitative evaluation can be made from table 3 by means of the percentage disturbing coefficients for each scalar lead, or a specific illustration may be found in figure 6. The relative amplitudes of these systems are also in error, but, by the use of empirical standardization factors, these may be corrected for, to a partial extent. In view of this comparison which applies for a homogeneous torso with a dipole in the center of the heart, it would seem clear that the systems of Duchosal and Grishman do not warrant further study, since it is extremely unlikely that nondipolar properties of the human heart generator and inhomogeneities of the body could conceivably offset the intrinsic defects shown in the torso model. Moreover, it should be remembered that Duchosal and Grishman, along with most vectorcardiographers, postulate a dipole for the heart and assume a homogeneous medium.

On the other hand, the relatively good agreement in scalar-lead shape for all three leads of the Wilson system, resulting from a fortuitous set of conditions, suggests that the scale factors experimentally determined for the torso might be applied to the Wilson system with substantial improvement. The scale factors which are more nearly appropriate, based on the model results for this particular dipole position, are given in figure 8 with the corresponding modified vector loops. Specifically, $V_L - V_R$ and $V_B - V_C$ are recorded at equal amplification while $V_F - V_C$ is recorded at 3/4 the amplification of the other two.* The other two systems cannot be improved to this extent by modifying the scale factors, and it is very important to appreciate just why the modified Wilson system gives results that are as satisfactory, as shown in figure 8. It is *not* because the theory of a centric dipole in a homogeneous conducting sphere is accurately applicable to the human torso, since, as has been shown, the tetrahedron in image space departs drastically from that inscribed in the theoretical model of Wilson. The good agreement is traceable to two factors: First, the Wilson central terminal volt-

* The standardization factors suitable for a female torso with a dipole in the center of the heart differ by 10 per cent or less from those given for the male torso.

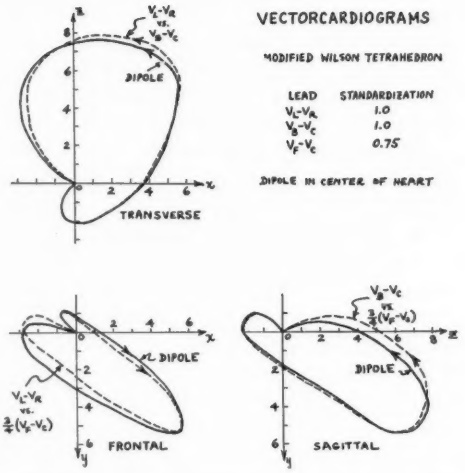

FIG. 8. Vectorcardiograms obtained in a homogeneous torso with a dipole fixed in position in the center of the heart, using modified standardization factors for the Wilson tetrahedron, are compared with projections of the dipole variations. The relative agreement between recorded variations and actual dipole variations is approximately 20 per cent or better for this dipole position.

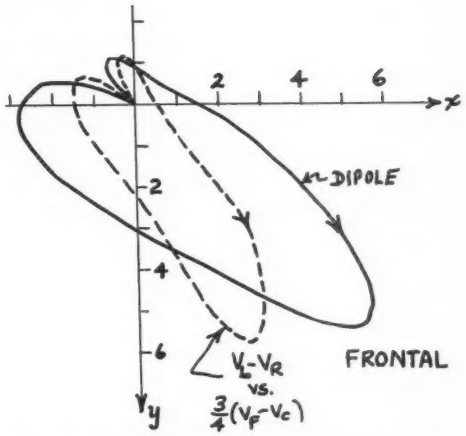

FIG. 9. The influence of dipole position is illustrated for a frontal-plane vectorcardiogram using the modified Wilson system of figure 8. The dipole position used here was shifted from that in figure 8 in the following manner: 2.4 cm. to the left (x direction), 2.4 cm. toward the foot (y direction) and 1.5 cm. toward the anterior chest ($-z$ direction). The largest error is in V_L-V_R which is more susceptible to dipole positional changes than V_F-V_C; the former error depends upon the partial cancellation of p_y and p_z in the equation for V_L-V_R, while the latter error depends upon the degree to which the Wilson central terminal potential shifts as a result of the dipole positional change. Any system of vectorcardiography using the same body-electrode positions regardless of heart position is vulnerable to errors of the type illustrated.

age deviates from the dipole midpotential in such a way as to tend to offset the errors that would otherwise be obtained, and second, the orientation of the vector from R to L in image space tends to give error cancellation to a fair degree for this particular dipole position. The effectiveness of these lucky error-cancellation tendencies depends to some extent on the shapes of p_x, p_y and p_z and more markedly upon the dipole position, as has been emphasized elsewhere.[12, 16] Generally, the potential difference between R and L is more susceptible to errors of dipole position, torso shape and dipole functions than are the potential differences between F and C, and B and C.

An illustration of the dependence on dipole position is given in figure 9 for the frontal-plane vector loop, using the same p_x, p_y and p_z as in figure 8. The angle at which the manifest heart vector is a maximum is, in this case, 65 degrees as compared with the true angle of 44 degrees at which the heart dipole magnitude, as seen in the frontal plane, is a maximum. This discrepancy is considerable despite the use of the same standardization factors which gives good agreement for a dipole in the center of the heart.

Viewing the image surface as a whole, it is possible to determine torso electrode positions which are substantially perfect for recording faithfully the variations of the separate dipole components; to a degree which is superior to that of the modified Wilson tetrahedron.[10, 17] However, when the dipole position or torso shape is changed, these same electrode positions are no longer as accurate. Any system of fixed electrode placement for all subjects will be vulnerable to errors traceable to torso shape variations and dipole positional changes. However, it can be seen from the results presented here that the central terminal can be used to advantage in such a way as to offset the effects of dipole position to some extent. In fact, an extremely important practical principle can be formulated; namely, systems which do not employ a central terminal, or do not pool the electrodes together in some fashion, are more highly vulnerable to dipole positional changes from subject to subject, and within the same subject, than those which take advantage of the averaging effects of a central terminal of

some kind. This principle has nothing to do with whether the central terminal is at the dipole midpotential or not; indeed, the compensating effects of the central terminal come about for the very reason that the junction is not at the dipole midpotential. Since the Wilson tetrahedron incorporates this important feature and, moreover, since it utilizes standard electrode positions which are easily determined and reproduced, and for which a huge amount of correctable empirical data already exist, it would appear to show future promise as a practical system of electrode arrangement for vectorcardiography, and deserves further study.

The applicability of these results to the human subject is, of course, a crucial question, since in these studies only the effects of dipole position and torso shape were considered. This question is currently being explored on human subjects in this laboratory in general terms for all body electrode positions, not confined to any particular system of electrode placement.[10] The applicability to the human subject of the results presented here may be investigated by recording body-surface voltages using all three systems and analyzing the results using the equations in table 2. If the torso results are accurately applicable to the human subject, the results so analyzed for each of the three systems should all agree. Lack of agreement may not be conclusive because the subject may not have the same dipole position as that used to obtain table 2 (torso data for other dipole positions may, of course, be determined experimentally), and the subject's torso shape may differ from that shown in figure 3. On the other hand, if these factors are properly taken into account, lack of agreement could then be attributed to errors in the fixed-dipole assumption, to human body inhomogeneities, or to faulty experimental technique which is entirely possible in view of the many variables which disturb the measurements such as body-loading by the recording system, respiratory changes, finite electrode size, and other similar factors. Conclusions based upon the torso-model results presented here must be used cautiously until further information concerning the additional assumptions is obtained.

However, there is strong evidence provided by unpublished data that the male torso model results are very nearly applicable to the normal human subject on whom the model was moulded. It has been demonstrated, using a generalization of the technic of Schmitt,[7] that QRS body-surface potentials on this subject (and on several other normals as well) contain less than 5 per cent nondipolar effects; that is, QRS body-surface waveforms are predictable to 95 per cent accuracy or better by means of the dipole concept. This statement applies to both precordial and distant electrodes. Moreover, the amplitude and shape of measured instantaneous QRS complexes at a wide variety of electrode sites over the entire torso of this normal male agree to within approximately ± 15 per cent with potentials predicted from his torso model coefficients, thus indicating that the influence of human-body inhomogeneities is not excessive.

Despite these complications, the study of this simplified model of the human electrical system which takes into account at least some of the important factors governing the relationship between the human heart and the body surface potentials it produces, has served to show that certain systems of vectorcardiography are significantly inferior to others. In addition it has been possible to establish a quantitative estimate of the smallest errors that might be expected in human vectorcardiography.

Summary

1. Three commonly used systems of vectorcardiography are studied using a homogeneous male torso with a dipole fixed in position in the center of the heart.

2. A direct quantitative comparison of each system with the known dipole behavior is made in terms of equations, geometric interpretations, scalar leads and vectorcardiograms.

3. It is found that the scalar lead shapes of the Wilson tetrahedron deviate, on the average, by approximately 15 per cent from the torso dipole variations, but the scalar lead shapes of the systems of Duchosal and Grishman show significantly larger discrepancies.

4. It is found that the standardization factors presently employed in the Wilson system are too large, particularly with respect to the head-to-foot dipole component (by a factor of 2.3). Certain standardization factors of the other two systems are considerably greater in error.

5. It is concluded that the accuracy of the

three systems as presently used is unsatisfactory, and that the systems of Duchosal and Grishman show least promise.

6. Certain fortuitous features of the Wilson system enable a modification of the standardization factors which leads to results that are fairly satisfactory for a dipole located in the center of the heart. This system, which possesses certain other advantages, would appear to deserve further study.

7. The applicability of these conclusions to the human subject depends upon the degree to which the behavior of dipole potentials in a homogeneous torso may be applied to humans. Methods of ascertaining this applicability are indicated.

Sumario Español

1. Tres sistemas comunmente usados en vectorcardiografía han sido estudiados usando un torso homogéneo masculino con un dipolo fijo en posición en el centro del corazón.

2. Una comparación cuantitativa directa de cada sistema con la conducta conocida del dipolo se hace en términos de equaciones, interpretaciones geométricas, derivaciones escalares y vectorcardiogramas.

3. Se encuentra que las configuraciones de las derivaciones escalares del tetraedro de Wilson desvían como promedio por aproximadamente 15 por ciento de las variaciones del dipolo del torso, pero las configuraciones de las derivaciones escalares de los sistemas de Duchosal y Grishman muestran discrepancias relativamente mayores.

4. Se encuentra que los factores de normalización presentemente empleados en el sistema de Wilson son muy grandes, particularmente con respecto al componente de dipolo céfalocaudal (por un factor de 2.3). Algunos factores de normalización de los otros dos sistemas son considerablemente mayores en error.

5. Se concluye que la precisión de los tres sistemas como usados en el presente no es satisfactoria, y que los sistemas de Duchosal y Grishman muestran la menor promesa.

6. Algunos rasgos fortuitos del sistema de Wilson proveen una modificación de los factores de normalización que conllevan a resultados que son bastante satisfactorios para un dipolo localizado en el centro del corazón. Este sistema que posee algunas otras ventajas aparenta merecer más estudio.

7. La aplicabilidad de estas conclusiones al sujeto humano depende en el grado en que la conducta de potenciales dipolo en un torso homogéneo pueda ser aplicado a los humanos. Métodos para determinar esta aplicabilidad son indicados.

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CLINICAL PROGRESS

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The Heart In Renal Disease

By HARRY A. DEROW, M.D.

RECENT advances in our understanding of the pathologic and functional disturbances of the heart in renal disease have led to more rational and effective therapy. The purpose of this communication is to review this progress.

The relation between the renal disease and the cardiovascular disorder is variable. In some instances renal disease is primary, and causes secondary hypertension; these renal diseases are glomerulonephritis, pyelonephritis, polycystic disease. On the other hand renal disease may develop secondarily during the course of essential hypertension, simultaneously with rheumatic heart disease, or during the progress of subacute bacterial endocarditis. In diffuse visceral diseases, the kidneys and heart may be commonly affected as in amyloidosis, periarteritis nodosa, and lupus erythematosus. In diabetes mellitus, renal complications and hypertensive and arteriosclerotic heart disease may develop in succession. It is evident that a cardiac disorder may appear and constitute the major problem in management in the course of acute or chronic renal disease.

Recognition of Renal Disease

It is usually impossible to define precisely when a renal lesion appears in the above-mentioned conditions. Detection of a clinically significant degree of renal damage is usually less difficult. *Constant proteinuria is the fundamental diagnostic finding of clinical renal disease in the absence of congestive heart failure.*[1]

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Renal Function

In patients with renal disease, the functional status may be determined by urine concentration test, phenolsulfonphthalein excretion 15 minutes after the intravenous injection of 6 mg. of the dye, and the level of the blood nonprotein nitrogen. For clinical purposes one may consider that *normal renal function* is present when a concentration test yields urine of 1.026 or higher specific gravity; *impaired kidney function* is present if the maximal specific gravity is 1.018, the excretion of phenolsulfonphthalein is less than 25 per cent, and the blood nonprotein nitrogen is within normal limits (30 to 40 mg. per 100 cc.); *renal insufficiency* is present if the maximal specific gravity is 1.012, the phenolsulfonphthalein excretion is less than 5 per cent and the blood nonprotein nitrogen is 45 mg. per 100 cc., or higher.

Although clearance methods for the study of discrete renal functions have contributed significantly to our understanding of the physiology of kidney function in renal and cardiac disease, such technics are not readily adaptable for use in the clinic.

Intravenous or retrograde pyelography may be indicated to establish the presence of two kidneys, the functional capacity of each, deviations in gross size and shape, deformities in the calyceal architecture and obstructive phenomena. The diagnosis of unilateral renal disease can be made only by this method of investigation. The possibility of ureteral obstruction is of such paramount importance in patients with anuria that retrograde investigation by a skilled urologist is usually indicated.

Heart in Acute Glomerulonephritis

Patients with acute glomerulonephritis whom the physician is usually called upon to treat are

those who present overt phenomena such as gross hematuria, edema, heart failure, pulmonary edema, hypertension, cerebral phenomena, oliguria and anuria, a few days to four weeks after a streptococcal infection. The diagnosis under such conditions is not difficult. On the other hand, signs and symptoms suggestive of heart failure may mask the clinical picture to such an extent that the underlying renal condition may be overlooked.

In the initial stage of acute glomerulonephritis, the danger to the circulation is of primary importance; the commonest cause of death is heart failure.

Friedberg[2] and Derow[3] have recently reemphasized the important manifestations of cardiovascular disturbances in acute glomerulonephritis—that is, hypertension, cardiac enlargement, electrocardiographic abnormalities and heart failure.

Hypertension. Elevated blood pressure of variable severity is observed in many cases. Its cause remains unexplained. The role of hypertension in the development of cardiac enlargement and heart failure in acute glomerulonephritis is not as evident as its importance in causing encephalopathic phenomena.

Cardiac Enlargement. Hypertrophy frequently appears within the first week or two in acute glomerulonephritis. The enlargement is usually slight, but may be considerable when signs of severe heart failure occur. I have repeatedly observed by serial x-ray examinations the return to normal size of the cardiac shadow with the onset of spontaneous diuresis and the subsidence of the renal disease. No evidence of pericardial effusion has been found at autopsy to account for the enlarged cardiac silhouette seen on x-ray study. Dean[4] reported that cardiac enlargement may persist for many years after acute glomerulonephritis in spite of little or no elevation of the blood pressure; however, the possibility that the cardiac enlargement in his three cases antedated the nephritis cannot be excluded.

Although the cardiac enlargement is usually attributed to the hypertension, it has also been observed in the absence of elevation of the blood pressure. Gore and Saphir[5] stated that it is doubtful whether a presumably normal heart could enlarge to a weight of 500 Gm. in 10 days (their case 3) through muscular hypertrophy alone. In their study of 160 cases of acute and subacute glomerulonephritis, 16 patients were found to have cardiac enlargement and 14 of these presented the signs and symptoms of heart failure. The factor common to all the enlarged hearts in their studies was a patchy serous myocarditis. Such increases of interstitial fluid could increase the weight of the heart appreciably and rapidly. They and other observers[6, 7] suggested that increased capillary permeability was the underlying cause of the serous myocarditis. However, Christian[8] stated that "in fatal cases on which postmortem studies had been made no changes have been found in the myocardium of sufficient extent or degree to explain satisfactorily the cardiac condition observed during life." The finding of an underlying disorder of the myocardium in acute glomerulonephritis has not been sufficiently uniform to explain the cardiac enlargement in all cases.

The role of the expanded blood volume caused by retention of salt and water in acute glomerulonephritis in producing interstitial edema remains to be clarified.

Electrocardiographic Abnormalities. These occur more frequently than overt signs of heart failure in acute glomerulonephritis. Low or inverted T waves in lead I and in the precordial leads are the commonest changes. These abnormalities disappear with the subsidence of the renal lesion. Interstitial fluid accumulation resulting in electrolyte and other metabolic disturbances may account for the T-wave changes. Similar electrocardiographic changes may occur in cases of overdosage of desoxycorticosterone acetate.

Heart Failure. Failure, or a syndrome resembling it clinically, is the most frequent complication and the commonest cause of death during the initial stage of acute glomerulonephritis. Since a complex combination of factors may exist in such patients, it may be difficult to assess the role of each factor in the pathogenesis of the syndrome. Of the utmost importance is the fact that the clinical features of heart failure may appear in previously healthy individuals without a past history of cardiac

disease, and that with the onset of diuresis the apparent heart failure often disappears very rapidly as the size of the heart returns to normal. It is well known that manifestations of heart failure in acute glomerulonephritis may occur without significant hypertension; elevations of blood pressure may, however, precipitate heart failure.

The possible occurrence of an underlying metabolic disorder of the myocardium that might be of primary importance in the pathogenesis of heart failure in acute glomerulonephritis was discussed above. Davies,[9] however, on the basis of his studies, concluded that the evidence for the view that heart failure in acute nephritis is due to myocardial damage was not convincing.

Disturbances of electrolyte balance may result in altered function and decreased efficiency of heart muscle. Bradley[10] stated that although deficient excretion of sodium and water because of the primary renal disease results in an increased blood volume, it is probable that heart failure is rarely, if ever, induced by increase in blood volume; an underlying disorder of the myocardium must be present.

Recently, Davies[9] and Rosenheim[11] suggested that the phenomena of heart failure—that is, hypervolemia, elevated venous pressure, cardiac enlargement, pulmonary congestion and edema—and hypertension in acute glomerulonephritis are similar to those observed in cases of overdosage of desoxycorticosterone acetate (DOCA) or cortisone. They also stressed the rapid reversibility of the apparent heart failure in these conditions with the onset of diuresis.

The term "heart failure" in acute glomerulonephritis may be misleading since it calls attention to the heart as the cause of the phenomena mentioned above. Actually, the reduction of glomerular filtration owing to the glomerular lesion may result in sodium and water retention, hypervolemia, increased venous pressure, cardiac enlargement, hydrothorax, ascites, edema, dyspnea, orthopnea and attacks of pulmonary edema. In the opinion of Davies[9] the absence of previous history of cardiac damage, the normality of the cardiac output and circulation time, the rapid reversibility of heart failure with spontaneous diuresis, and the usual absence of histologic changes in the myocardium in fatal cases suggest that the heart is not primarily involved and that salt and water retention with resultant expansion of the blood volume may be the cause of the apparent heart failure.

Altschule[12] has suggested the term "natrigenic hypervolemia" to characterize the phenomena that resemble heart failure not only in cases of acute glomerulonephritis but also in patients suffering with overdosage of desoxycorticosterone acetate, corticotropin, or cortisone; the "central" fault is in the kidneys and not the heart. Friedberg's[13] observations on the occurrence of the clinical syndrome of congestive heart failure as a result of sodium and water retention in cases of carbon tetrachloride nephrosis without evidence of cardiac disease support this concept.

Stead[14] recently made the following statement: "The only way to tell whether a person with acute glomerulonephritis has heart failure is to measure the cardiac output and to relate it to the total oxygen consumption. If the cardiac output and mixed venous-arterial oxygen differences are normal, heart failure is not present, as this disease is not one of those which speeds up the circulation. If the venous-arterial oxygen difference is increased, mechanical heart failure is likely."

The occurrence of cardiac enlargement and acute pulmonary edema with dyspnea suggests the presence of acute heart failure. This clinical impression has, to date, not been substantiated by the necessary hemodynamic studies; indeed, such studies may not be performed because of the hazards to the patient under the circumstances. The heart failure might be due to metabolic disturbances that interfere with enzyme systems and normal contractility of the myocardium. The renal factor is undoubtedly of great importance and may be the primary cause of the heart failure.

Obviously, the pathogenesis of the apparent heart failure in acute glomerulonephritis is obscure and its clarification must await further study.

Treatment

Treatment is largely symptomatic in a disease such as acute glomerulonephritis in which the etiology is unknown and from which most patients recover. There is no known specific therapy that influences healing of the glomerular lesions and prevents progression from the acute to the chronic form of the disease. However, treatment based on current knowledge of the abnormal physiology of acute glomerulonephritis may be effective in the prevention and management of complications and major symptoms.

Heart Failure. The development of heart failure constitutes an emergency that may result in death in a small number of obviously severe cases of acute glomerulonephritis. Awareness of this serious complication, its prevention if possible and its early recognition and management make the active treatment of acute glomerulonephritis important.

While the mortality in the initial stage is in large measure related to the severity of the heart failure, the patient who survives this complication has as good a chance of complete recovery from acute glomerulonephritis as the one with the milder form of the disease.

Heart failure may be characterized by a sudden onset of dyspnea and orthopnea progressing to severe acute pulmonary edema. It may develop more insidiously and may involve the systemic as well as the pulmonary circulation.

The knowledge that the several pathogenetic factors are present to produce or simulate heart failure should emphasize the importance of the following measures:

Complete bed rest is essential during the initial stage of acute glomerulonephritis as long as heart failure, edema, hypertension, oliguria or anuria persist.

Diet and fluid intake should be carefully regulated in the initial stage. The "hunger and thirst treatment" of Volhard,[15] formerly widely practised, is now being supplanted by a diet containing 100 to 150 Gm. of carbohydrate, no sodium salts, and fluid restriction to the volume excreted by the kidneys, in addition to about 1000 to 1200 cc. lost by insensible perspiration. Intravenous infusions may precipitate or aggravate heart failure by increasing the blood volume. A more liberal diet and fluid intake are instituted after disappearance of heart failure, edema, hypertension and oliguria.

In the presence of impending or actual *pulmonary edema*, rapid venesection—500 cc. of blood in adults, and proportional amounts in children—should be done. In addition to venesection, early administration of oxygen by tent or positive pressure mask, and antifoaming agents should be employed in the treatment of severe pulmonary edema; morphine and atropine in adequate doses should also be given. Tourniquets on all four extremities may be employed. Tilting of the patient's head below the edge of the bed may relieve respiration by providing drainage of the pulmonary edema. At times, the suddenness and rapidity with which pulmonary edema develops preclude the use of any therapeutic measure to prevent death.

The rapid subsidence of the signs and symptoms of severe heart failure without the benefit of digitalis in these cases leaves the impression that the improvement is due to the spontaneous diuresis rather than changes in the contractility of the heart. The possibility also arises that the spontaneous diuresis signifies recovery from capillary and metabolic derangements. Although digitalis in a rapidly excreted form (such as Cedilanid and Digoxin) is recommended[16] by the oral or intravenous route, depending upon the urgency for the treatment of heart failure in acute glomerulonephritis, it is difficult to evaluate its effect.

There is no reliable method of treatment for freeing the obstructed glomeruli to initiate glomerular filtration. Diuretics are of no value and in fact may be harmful.

Hypertension. Frequent, careful determinations of blood pressure should be made in all cases of acute glomerulonephritis. However, not all patients who have an elevated blood pressure exhibit hypertensive complications. Gradual or sudden rise of the blood pressure sometimes provides objective evidence of the imminence of heart failure. In spite of the fact that the pathogenesis of heart failure in acute

glomerulonephritis remains to be clarified, the development of severe hypertension may either precipitate heart failure or aggravate already existing failure.

The reduction of the blood pressure to normal levels will at least serve to eliminate the hypertensive factor in the genesis of the heart failure. Sometimes the return of the blood pressure to normal levels appears to contribute favorably to the patient's recovery from the heart failure. The dosage and frequency of administration of vasodepressor preparations depend upon the degree and duration of the hypotensive effect, the relief of the cardiac symptoms, and avoidance of toxic manifestations, including severe hypotensive collapse; dosage of vasodepressor medication must be individualized to obtain satisfactory results.

Magnesium sulfate administered orally, rectally, or parenterally is often effective in reducing the blood pressure. Because of the lack of any blood pressure lowering effects of magnesium sulfate in some cases, effective vasodepressor oral preparations of veratrum alkaloids and hydrazinophthalazine may be used in mild or moderately severe hypertension; in severer cases these medications may be given parenterally. Although a transient decrease in urinary volume is observed after the injection of veratrum alkaloids and hydrazinophthalazine, this decrease is not marked unless a profound hypotensive effect is produced by large doses of these drugs. The oliguria is accompanied by reduction of the glomerular filtration rate and of sodium and water excretion; these phenomena are transient. Even though the oliguria is usually followed by a marked polyuria, the reduction in function may be detrimental if continued for a prolonged period when azotemia is present.

Rapid venesection of 500 cc. of blood in adults and proportional amounts in children is sometimes effective in lowering the blood pressure. This procedure should not be employed in the presence of anemia.

Sedation is of great importance in these patients because of the restlessness, irritability and apprehension usually present. Small doses of phenobarbital are helpful not only in providing relaxation and rest but also in lowering the hypertension. Rectal administration of chloral hydrate or paraldehyde may be beneficial. However, it is sometimes necessary to resort to such drugs as Sodium Amytal in doses of 0.25 Gm. given intramuscularly or intravenously.

Heart in Acute Renal Failure

In the past few years, much has been written about acute renal failure, a syndrome characterized by severe oliguria or anuria and renal insufficiency. The varied etiology and pathogenesis of this syndrome, and the pathology and functional derangements of the kidney, have been described by many observers.[13, 17-20] Therapeutic regimens directed at the alleviation of nitrogen retention and the correction of electrolyte disturbances of the blood until the damaged kidneys recovered spontaneously have included the artificial kidney, peritoneal dialysis, intestinal irrigation and exsanguinotransfusion. The conservative management, without dialyzing procedures, has been improved greatly as a result of more thorough familiarity with the physiology of fluid balance, electrolyte relationships and protein metabolism. The purpose of all types of treatment of acute renal failure is to tide the patient with reversible urinary suppression over the critical anuric phase until spontaneous recovery and diuresis occur.

However, only recently has an appreciation developed of the fact that after the appearance of acute urinary suppression, cardiac failure is the most serious complication and the principal cause of death.[13, 17, 19, 20] Potassium intoxication, with abnormalities of cardiac conduction terminating in ventricular fibrillation or asystole, may also contribute to a fatal outcome.

Heart Failure

Friedberg[13] emphasized the fact that the deficient excretion of sodium and water in acute renal failure can produce the complete syndrome of congestive heart failure without cardiac disease. While the danger of fatal pulmonary edema due to massive intravenous infusions and the futility of such measures to overcome urinary suppression have been stressed and recognized, there is still inadequate

recognition of the frequency of edema and other evidences of congestive heart failure induced by the administration of moderate amounts of fluid which have no egress because of the complete or almost complete cessation of renal excretion of sodium and water.

There may be some question about the applicability of the term "congestive heart failure" to cases of acute renal failure in which there is no clinical, electrocardiographic or pathologic evidence of cardiac disease and no previous history suggesting cardiac damage. Nevertheless, at some stage in the clinical course most or all of the cardinal features of congestive heart failure may occur in patients with acute renal failure—dyspnea, orthopnea, attacks of pulmonary edema, engorged neck veins and elevated venous pressure, enlargement of the liver, subcutaneous edema, hydrothorax, ascites and gallop rhythm. In patients with pronounced pulmonary congestion the second pulmonic sound is accentuated. As in cases of congestive heart failure associated with the common cardiac diseases, the symptoms may be precipitated or intensified by sodium-containing fluids and alleviated by sodium and fluid restriction, or, in acute episodes, by phlebotomy.[13]

Although cardiac failure may be defined physiologically in terms of adequacy of the cardiac output, in practice it is defined as a clinical syndrome and is recognized by the above-mentioned clinical features.[13] From the latter viewpoint the criteria for "congestive heart failure" are fulfilled even though there is no evidence of underlying heart disease.

The circulation time in cases of acute renal failure with heart failure is normal or decreased. The circulating blood volume is usually increased and the venous pressure elevated.

Pathogenesis. In the usual type of congestive heart failure associated with chronic cardiac disease, the "central fault" lies in the heart.[21, 22] Myocardial weakness results in a deficient cardiac output as a consequence of which the blood flow to the kidneys is greatly reduced. Diminished glomerular filtration, increased tubular reabsorption, increased renal venous pressure and possibly other factors are responsible for the impairment of renal excretion of sodium and water. In acute renal failure, however, the "central fault" lies in the kidneys; the severe oliguria or anuria is also associated with reduced renal blood flow and deficient excretion of sodium and fluid.

Because of the impaired excretion of sodium and water in congestive failure due to underlying cardiac disease as well as acute renal failure, the administration of sodium-containing fluids may precipitate, and their restriction may alleviate symptoms in both conditions.

In acute renal failure, heart failure is perhaps due to metabolic or hemodynamic disturbances that interfere with enzyme systems and normal contractility of the myocardium. The renal factor is undoubtedly of great importance and may indeed be the primary cause of the heart failure.

Potassium Intoxication

The clinical manifestations, dangers and electrocardiographic changes of hyperkalemia and the methods for controlling it have become familiar in the past few years. Potassium intoxication seems to depend upon many factors beside the absolute serum concentration of potassium. Merrill and his associates[23] have shown that hyponatremia and acidosis aggravate the toxic effects of hyperkalemia. In acute renal failure, serial electrocardiograms and serial determinations of the concentration of serum potassium, sodium and carbon dioxide combining power provide adequate warning of progressing hyperkalemia and potassium intoxication. The clinical manifestations of potassium intoxication seldom appear before the condition is advanced and a fatal outcome is imminent.

Hyperkalemia develops in most cases of acute renal failure if potassium salts, fruit juices and protein are administered or as a result of liberation of potassium by rapid catabolism of tissue protein, hemolysis or injury to muscle. Even though potassium intoxication—an elevation of the concentration of serum potassium above 8.0 mEq. per liter and the appearance of characteristic electrocardiographic changes beyond mere "peaking" of T waves—develops less often, it may prove to be fatal when present.

Electrocardiographic Changes. The electrocardiographic abnormalities of hyperkalemia may be simulated or modified by hyponatremia and acidosis. With serum potassium levels in excess of 6 mEq. per liter the T waves become tall and pointed, a configuration termed "peaking" or "tenting." [20] With levels above 8 or 9 mEq. per liter, prolongation of the P-R and QRS intervals and decreased amplitude and disappearance of the P wave occur. With higher levels of potassium, the T wave decreases in amplitude, the QRS complex and T wave merge; paroxysms of abnormal ventricular rhythms and periods of asystole may appear.

Treatment

In the management of acute renal failure, treatment should be planned to prevent congestive heart failure and potassium intoxication since these complications are most apt to cause death. The details of such therapy have recently been presented by Friedberg,[13] Stock,[19] and Swan and Merrill.[20] The need for individualizing the management because of the variability of the clinical course of acute renal failure must be emphasized; also, that diuresis and recovery usually occur spontaneously within two weeks provided the patient can be tided over the critical anuric phase of the syndrome.

Since the details of therapy of acute renal failure are available to the reader in the reports of the above mentioned observers, only a summary will be presented here with special emphasis on the prevention and treatment of congestive heart failure and potassium intoxication.

Heart Failure. Because of the reduced tolerance for sodium in acute renal failure, the use of sodium-containing fluids to correct hyponatremia, hypochloremia and acidosis may precipitate cardiac failure. No sodium should be administered in any form until diuresis is established because these electrolyte disturbances constitute only minimal risks. Stock[19] on the other hand has carefully used small amounts of alkali to correct these abnormalities in part without precipitating congestive failure.

In acute renal failure the body has no satisfactory mechanism for removing fluid administered in excess of the amount of insensible loss, that is, about 1000 cc. Much harm may be done by the administration of large or moderate quantities of fluid, parenterally or orally; increased blood volume with cardiac failure, peripheral edema, pulmonary edema and death may occur. The amount of fluid given should replace only that amount of fluid lost by the body and no more. This requires an estimation of insensible water loss, careful measurement of any urine, all vomitus, diarrheal stools, loss by saliva (in cases of mercurial stomatitis); the total daily fluid deficit, volume for volume, should be replenished.[19]

The correction of anemia by small frequent transfusions may result in pulmonary congestion. The use of infusions of packed cells reduces this hazard.

The rapid subsidence of the signs and symptoms of heart failure without the benefit of digitalis in these cases leaves the impression that the improvement is due to the spontaneous diuresis rather than changes in the contractility of the heart. The possibility also arises that the spontaneous diuresis signifies recovery from metabolic and capillary derangements. In the author's experience the effect of digitalis in the management of "congestive heart failure" in acute renal failure has been difficult to evaluate.

Mercurial diuretics and acidifying salts are to be avoided in view of the presence of the kidney damage, azotemia and acidosis.

If pulmonary edema develops as a result of the excessive or moderate administration of sodium-containing fluids the management of the patient should include the measures described above in the "Heart in Acute Glomerulonephritis."

Potassium Intoxication. The measures that may be employed to reduce threatening levels of plasma potassium concentration are the administration of glucose and insulin to bring about a shift of potassium into the cells of the liver and muscles, the use of cation exchange resins and intestinal irrigation to promote gastrointestinal losses of potassium, and the employment of dialysis with a perfusion fluid low in potassium.[19, 20] Dialyzing technics have recently been so improved that in the event

that potassium intoxication does not respond to conservative management, the use of the artificial kidney may be indicated.

Heart in Chronic Renal Disease

Cardiac involvement in chronic renal disease is usually the result of hypertension and associated coronary arteriosclerosis. However, nonhypertensive heart disease as well as cardiac damage due to amyloidosis, lupus erythematosus and periarteritis nodosa may coexist with chronic renal disease. Only rarely does the heart escape damage in primary chronic renal disease until advanced renal insufficiency develops.

Renal Function in Chronic Renal Disease

Normal renal function may persist throughout the course of chronic renal disease, and death may be due to nonrenal causes. In cases of unilateral renal disease of inflammatory, vascular or congenital origin, total renal function may be normal. Impaired renal function may develop during and persist throughout the course of chronic renal disease. However, after a variable period, renal insufficiency may supervene. Uremia is by far the commonest cause of death in primary renal disease, such as glomerulonephritis. In chronic renal insufficiency, anemia, electrolyte disturbances and acidosis occur frequently. Furthermore, chronic renal insufficiency may be complicated by acute renal failure if dehydration with resultant reduction of blood volume is prolonged and untreated.

Hypertension and Coronary Arteriosclerosis

The cause of hypertension in chronic renal disease is unknown. The role of hypertension, primary or secondary, in the development of cardiac involvement has been known for many years.[24, 25] As a result of increased work imposed upon the heart, it dilates and hypertrophies as the work either continues or increases. Hypertension and coronary arteriosclerosis are intimately and frequently associated. Heart failure, angina pectoris and other manifestations of coronary insufficiency may develop during the course of the hypertensive-renal disease. Primary hypertension may be present for many years with gradual development of cardiac manifestations; renal insufficiency appears in only a small number of such cases. On the other hand, in cases of chronic renal disease with secondary hypertension, acceleration of the destruction of the renal parenchyma due to the addition of renal arteriolosclerosis, may result from the elevated blood pressure, especially if it is severe and continuous. However, the progress of the renal disease may be slower than the development of cardiac involvement, so that heart failure, angina pectoris or other manifestations of coronary insufficiency may develop before renal insufficiency appears. In many cases of chronic renal disease, cardiac manifestations occur during the stage of impairment of renal function and may precipitate acute renal insufficiency as a result of the oliguria of congestive failure, or the peripheral circulatory collapse of myocardial infarction. Furthermore, in chronic renal insufficiency, cardiac failure or myocardial infarction may supervene and aggravate the already existing renal insufficiency.

Patients may die in uremia without congestive heart failure at a time when the heart is enlarged and severe anemia, acidosis and pericarditis are present.

The supervention of the syndrome of malignant hypertension during the course of primary or secondary hypertension usually accelerates the tempo of the hypertensive disease with early development of cardiorenal problems.[26, 27] Hypertension, occasionally of the malignant form, may mask underlying unilateral renal disease and be responsible for a clinical picture that is essentially cardiac.

Cardiorenal problems similar to those described above are also seen in diabetes mellitus because of the frequent association of coronary arteriosclerosis and renal disease and in various forms of nonhypertensive heart disease including amyloid and collagen diseases coexisting with renal disease.

Treatment of Hypertension. The treatment of hypertension in chronic renal disease without renal insufficiency may be undertaken to prevent or reduce the strain upon the heart. Curative forms of hypertension should be looked for; nephrectomy for unilateral renal disease

and the surgical removal of a pheochromocytoma in cases of sustained hypertension may lower the elevated blood pressure to normal.

Drugs, diet therapy, and sympathectomy, either singly or in various combinations, have been successful in reducing the elevated blood pressure in many patients with consequent lessening of the strain upon the heart. However, abrupt, severe and prolonged hypotensive collapse is an occasional hazard of this type of therapy; it may lead to impaired circulation to the heart, brain and kidneys. Coronary occlusion or myocardial infarction may result in patients with coronary artery disease. The development of shock may be followed by acute renal failure.

In chronic renal insufficiency, therapy directed to diminish the hypertension is often hazardous because of the delayed excretion of drugs with severe toxic potentialities, and the worsening of existing electrolyte derangements. However, it may be possible to reduce the azotemia and slow the progress of the renal disease by moderate lowering of the severe hypertension in chronic renal insufficiency. Although sympathectomy has afforded symptomatic relief in some of these patients,[28] this procedure is usually contraindicated.[29]

Anemia

A normocytic, normochromic anemia almost always develops in chronic renal insufficiency; there is, however, not always a correlation between the levels of azotemia and the degree of anemia. The cardiac adjustments in chronic anemia and their clinical manifestations have been described by Blumgart and Altschule[30] and others.[31]

Cardiac enlargement occurs more frequently in patients with very low levels of hemoglobin. Electrocardiographic changes of minor degree occur, and may signify anoxia, coexistent coronary arteriosclerosis and degenerative changes in the myocardium. Angina pectoris may develop with severe anemia and is almost always associated with coronary arteriosclerosis. Congestive failure may occur because of "the necessity for the maintenance of the cardiac output and cardiac work at an abnormally high level for long periods of time, and the delivery to the myocardium of blood deficient in oxygen."[30] Factors favoring congestive failure in anemic patients are coronary arteriosclerosis and hypertension.

Edema may develop in anemia even in the absence of heart failure. Delayed excretion of sodium, varying in degree with the severity of the anemia occurs[32] and is perhaps a result of the markedly reduced renal blood flow.[33]

Dyspnea is not necessarily a manifestation of heart failure since it may also be consequent to anemia. A variety of mechanisms favors hyperventilation and contributes to dyspnea in anemia. In addition the high cardiac output at rest reduces the cardiac reserve available for exercise and thereby favors exertional dyspnea.

It is clear that the anemia of chronic renal insufficiency may be responsible for some clinical cardiac manifestations. The coexistence of organic cardiac disease and the added strain upon the heart due to anemia and anoxia of the myocardium are especially prone to result in congestive heart failure, angina pectoris, coronary failure, or myocardial infarction.

Electrolyte Disturbances and Acidosis

Changes in the chemical composition of body fluids result from failure of renal regulation in chronic renal insufficiency.[34, 35] Dehydration and disturbances of acid-base adjustment and of maintenance of balance among various ions is evident in the distortions of the chemical structure of the plasma and the extracellular fluid. The ions usually affected are sodium, chloride, bicarbonate, calcium, sulfate and phosphate. Changes in the concentration of potassium may occur but are of minor importance unless oliguria and anuria develop. Dehydration reduces plasma volume and may lead to peripheral circulatory collapse and the clinical picture of acute renal failure. Acidosis in chronic renal insufficiency develops as a result of retention of sulfate, phosphate and probably organic acids and from the cessation of ammonia production and the loss of sodium. The sodium loss is associated with loss of bicarbonate and chloride. These changes may be aggravated and severe acidosis precipitated by the administration of acidifying salts such as ammonium chloride and other substances such

as renal carbonic anhydrase inhibitors and cation exchange resins employed in the treatment of congestive heart failure. Hypocalcemia develops as a result of phosphate retention and a decrease in absorption of calcium from the gastrointestinal tract as well as the obligatory renal excretion of fixed base.

The electrolyte disturbances and acidosis in chronic renal insufficiency may be responsible for cardiac manifestations such as disturbances in rhythm and in electrocardiographic pattern.

Alterations in the concentration gradient across the myocardial cell of sodium, potassium, bicarbonate and hydrogen ions and perhaps other components may result from electrolyte derangements. Since myocardial function is ultimately dependent upon processes by which depolarization and repolarization occur in sequence with systole and diastole, severe alterations in electric potential may result in cardiac failure.[36]

Hyperpnea or Kussmaul breathing, is one of the most striking manifestations of the acidosis of chronic renal insufficiency; its cause appears to be the lowered pH of the fluid bathing the respiratory center.

The coexistence of organic heart disease in chronic renal insufficiency and the added strain upon the heart consequent to electrolyte derangements, acidosis and anemia may cause congestive failure. Peripheral circulatory collapse with acute renal failure as a result of dehydration or myocardial infarction may further complicate and aggravate the electrolyte disturbances.

Uremic Pericarditis

Uremic pericarditis occurs in the terminal stage of renal insufficiency; its cause is unknown. Pathologic studies reveal pericarditis in more than half the cases of chronic renal insufficiency. Although acute fibrinous or serofibrinous pericarditis is usually found, there may be sterile serofibrinous or hemorrhagic effusions. Organization of the exudate and almost complete obliteration of the pericardial sac may occur. Occasional cases show slight degeneration and mononuclear infiltration of the myocardium beneath the layer of pericardial exudate. Although the pericardial exudate is almost invariably sterile, a terminal bacterial infection may be present in rare instances.

The pericarditis is usually asymptomatic; however, in some patients precordial distress with radiation to the shoulders may be present. In rare cases, the precordial discomfort may be severe and associated with slight fever, leukocytosis, fall in blood pressure, friction rub and electrocardiographic changes; such a picture may closely simulate myocardial infarction. The diagnosis of pericarditis is made on the basis of an audible friction rub varying in character from extremely soft and evanescent to coarse and persistent; the sounds are usually heard in the precordial area and rarely in the left interscapular region. Electrocardiographic changes of pericarditis may be seen in those cases in which the myocardium is involved beneath the pericardial exudate. Pericarditis usually appears shortly before death but survival for months or longer may take place[25, 37].

Electrocardiographic Abnormalities

Electrocardiographic abnormalities occur frequently in chronic renal disease.[2, 38] In the absence of renal insufficiency, changes consistent with left ventricular hypertrophy and myocardial damage are often seen in those cases associated with hypertension and coronary arteriosclerosis. In patients without an elevated blood pressure, the electrocardiogram is usually normal unless other forms of heart disease coexist.

Electrocardiographic abnormalities arise in chronic renal insufficiency as a result of anemia, electrolyte disturbances—hypocalcemia and hypopotassemia—acidosis and pericarditis. In addition to these changes, those associated with hypertension and coronary arteriosclerosis may be found. Abnormalities consistent with hyperkalemia may develop if acute renal failure supervenes. The electrocardiogram sometimes shows a complex picture that is difficult to interpret. On the other hand, in spite of severe electrolyte derangements, the electrocardiogram may be normal in the absence of hypertension and pericarditis.

"Uremic Edema" of the Lungs

A characteristic roentgenologic picture has been described[39] in some patients with renal insufficiency: symmetric dense opacities that fan out from both hilar regions like the wings of a butterfly; the apexes and the peripheral and basal portions of the lungs are usually clear; the outer borders of the "butterfly" opacities may be poorly or sharply defined. These densities change rapidly or disappear completely within a short time. The curious "butterfly" distribution of the radiologic lesions has not been satisfactorily explained.

Pathologic studies have revealed edema of the lungs associated with a fibrinous or albuminous alveolar exudate; hyalinization of the exudate is seen in the more advanced cases. Although infection rarely appears to be a factor in the development of these findings, left ventricular failure is usually present.

Physical findings are often minimal. These patients may present no symptoms except slight cough; in the more advanced cases, severe dyspnea may develop and contribute to the death of the patient.

Nephrotic Syndrome

The nephrotic syndrome characterized by massive proteinuria, hypoalbuminemia and hypercholesterolemia with or without edema, occurs most often during the course of glomerulonephritis, diabetes mellitus and amyloidosis. The prolonged elevation of the serum cholesterol in the nephrotic syndrome of glomerulonephritis is considered to be one of the factors responsible for the development of coronary arteriosclerosis in a young age group in which arteriosclerosis is relatively rare.[40] Myocardial infarction in young nephrotics has been observed.

The nephrotic syndrome with edema, especially in elderly patients with diabetes mellitus, may coexist with or simulate congestive heart failure. The differential diagnosis is often difficult.

Angina Pectoris, Coronary Failure, and Myocardial Infarction

Angina pectoris, coronary failure and myocardial infarction occur in chronic renal disease most often as a result of coronary arteriosclerosis. Rarely, in diffuse visceral diseases with cardiorenal involvement—such as, periarteritis nodosa and amyloidosis—these clinical disturbances of the heart may also develop. Excellent expositions of the pathogenesis, diagnosis, prognosis and therapy of angina pectoris, coronary failure and myocardial infarction have recently been presented by Blumgart[41] and Friedberg.[2]

Patients with cardiac pain and chronic renal disease with normal kidney function should usually be treated in the same manner as those without renal disease. However, if renal insufficiency coexists with coronary artery disease, anemia, especially when severe, may cause angina pectoris by increasing the work of the heart. In some of these patients, correction of the anemia by carefully administered transfusions of packed red cells may be followed by amelioration or even disappearance of cardiac pain.

The development of acute myocardial infarction in chronic renal insufficiency is catastrophic. In such cases with anemia and shock, the coronary blood flow is reduced because of the lowered blood pressure; the oxygen supply to the myocardium is still further lessened because of the anemia. In addition, shock is also responsible for the deprivation of the blood supply to the kidneys and the consequent supervention of acute renal failure. Not infrequently shock and pulmonary edema may appear simultaneously. The management of such patients is extremely difficult. The treatment of shock by the use of pressor amines, such as norepinephrine should be instituted immediately. It should be remembered, however, that intravenous infusions may aggravate existing pulmonary edema. The volume and rate of flow of the infusion should be carefully watched and held to the smallest quantity necessary to correct the hypotension. Because of the presence of anemia, venesection is contraindicated for the treatment of the pulmonary edema. In general, the principles of therapy described above under "Acute Renal Failure" should be followed. Drug therapy should be undertaken with extreme caution since excretion of all medications may be delayed to such

a degree that toxic blood levels ensue. Electrolyte derangements, acidosis and anemia present difficult therapeutic problems. Anticoagulant therapy is contraindicated because of the danger of hemorrhage as a result of the delayed excretion of the drugs.

In the absence of shock or pulmonary edema, myocardial infarction in cases of chronic renal insufficiency may be managed with the usual forms of therapy except anticoagulants. Such patients require close supervision for the recognition and cautious correction of electrolyte disturbances, acidosis and anemia.

Arterial embolization and renal infarction may develop consequent to myocardial infarction in rare cases; in the presence of chronic renal insufficiency, such an occurrence may be disastrous.

Congestive Heart Failure

Congestive heart failure in chronic renal disease is usually the result of hypertension and coronary arteriosclerosis; less commonly it is due to rheumatic heart disease and cardiac involvement associated with amyloidosis and collagen diseases. In chronic renal insufficiency, anemia, electrolyte derangements and acidosis are added strains upon the heart and contribute further to the development or aggravation of congestive heart failure.

The concept that congestive heart failure develops whenever the cardiac output becomes inadequate for the metabolic needs of the body has been widely accepted.[21, 22] Studies of the cardiovascular renal hemodynamics and metabolic interrelationships have shown that congestive heart failure is a consequence of changes in pressure-flow relationships in the circulation and disturbances in fluid and electrolyte metabolism, which lead to retention of sodium and water and the development of edema.[22] The changes in fluid and electrolyte metabolism in congestive heart failure are the result of a number of complex mechanisms such as impaired renal hemodynamics, changes in tubular function, increased adrenocorticotrophic activity, and increased renal venous pressure, which are activated when the cardiac output becomes inadequate.

Dyspnea. In chronic renal insufficiency, dyspnea is not always cardiac in origin but may be due to severe anemia, acidosis, and cerebral anoxia; it may be difficult to differentiate the various factors responsible for the dyspnea. Congestive heart failure may be complicated by these phenomena and give rise to more severe dyspnea.

Edema. In chronic renal disease edema may be due to congestive heart failure, the nephrotic syndrome and severe anemia in renal insufficiency. Often, congestive heart failure may be superimposed upon the nephrotic syndrome and renal insufficiency.

Renal Function. Oliguria, proteinuria and azotemia commonly occur in congestive heart failure. If the urinary specific gravity is high (1.026 or more) these findings may be due to heart failure, per se, or heart failure in association with chronic renal disease and normal kidney function. With diuresis and restoration of cardiac compensation, proteinuria and azotemia disappear if these manifestations are the result of heart failure, per se; proteinuria persists despite disappearance of azotemia if chronic renal disease with normal kidney function is present. On the other hand, if the urinary specific gravity is in the vicinity of 1.018 during the oliguric-azotemic phase of congestive heart failure, impaired renal function is probably present even if the azotemia disappears with diuresis and restoration of cardiac compensation. Furthermore, if the urinary specific gravity is 1.012 or less during the oliguric-azotemic phase of congestive heart failure, significant renal insufficiency is probably present; with diuresis and restoration of cardiac compensation the azotemia persists, usually in a lesser degree.

Treatment. Kidney function should always be carefully evaluated before therapy of congestive heart failure in chronic renal disease is undertaken. Patients with chronic renal disease and normal kidney function may be treated in the same manner as those patients with congestive heart failure without renal disease. Excellent presentations of the management of congestive heart failure have recently appeared.[2, 21, 22]

However, if either impaired renal function or renal insufficiency is present, the intelligent

management of congestive heart failure requires the awareness and recognition of the underlying abnormal physiology. Careful appraisals of the electrolyte equilibrium and the hemoglobin level are essential. Drug therapy should be undertaken with extreme caution since excretion of all medications may be delayed to such a degree that blood levels toxic to the patient ensue. Furthermore, measures employed to promote the excretion of salt and water and re-establish the balance between electrolyte and fluid intake and output may be responsible for electrolyte disturbances or for the aggravation of already existing electrolyte derangements.[42] Besides, steps taken to correct the anemia and acidosis of chronic renal insufficiency may aggravate the existing cardiac problem by the development of pulmonary edema.

Intractability of congestive heart failure in chronic renal insufficiency is a common occurrence because of the difficulty in instituting a suitable program to restore cardiac compensation without aggravating the existing renal insufficiency, electrolyte derangements and cardiac failure. However, in spite of these problems, it is possible to improve the cardiac failure in some patients without intensifying the underlying renal insufficiency by the use of digitalis, dietary sodium restriction, mercurial and other diuretics, electrolyte replacements, transfusions of packed red cells, and the avoidance of administration of ammonium chloride, renal carbonic anhydrase inhibitors and cation exchange resins. *The need for individualization in management cannot be overemphasized.* If renal insufficiency is severe as a result of chronic renal disease, measures employed for the restoration of cardiac compensation may be without any effect. In elderly diabetics, congestive heart failure may coexist with organic renal disease manifested by the nephrotic syndrome and renal insufficiency. The therapeutic approach in such patients is indeed a dilemma. Equally unsatisfactory is the management of the patient with chronic renal insufficiency and congestive heart failure who develops acute renal failure as a result of myocardial infarction or severe dehydration consequent to vomiting or diarrhea.

Emotion and the Heart in Chronic Renal Disease

Emotional disorders often coexist with cardiac and renal disease in many patients. In such cases, determination and evaluation of the causes of the multiple symptoms may be extremely difficult. Responses of the cardiovascular system to stress-producing situations include a change in heart rate, rise in blood pressure, increase in cardiac output, change in the contractile state of the blood vessels of the skin, and alteration in the respiratory rate and depth. Under emotional stress patients may complain of dyspnea, palpitation, chest pain, faintness and fatigue. Such complaints are not easy to evaluate in the presence of cardiac and renal disease. For example, the respiratory difficulty of anxiety is to be differentiated not only from the dyspnea of congestive heart failure but also from that due to anemia and acidosis in chronic renal insufficiency. Similarly, the chest discomfort of neurosis is to be distinguished from that due to coronary arteriosclerosis and uremic pericarditis. Faintness and fatigability may not only be caused by emotional disturbances but by congestive heart failure as well as the anemia of chronic renal insufficiency. Obviously, the appraisal of these complaints is difficult and can only be made on the basis of both the clinical and laboratory data and available information about the patient's personality.

Altschule[43] and others[44, 45] have emphasized the facts that the physiologic effects of emotion may exacerbate cardiovascular disease, that these manifestations may resemble those of coronary sclerosis and myocardial insufficiency, and that their occurrence may call attention to the presence of emotional disorders not previously recognized. In renal disease, symptoms associated with pericarditis, anemia and acidosis may further complicate the picture by causing manifestations difficult to distinguish from some of those encountered in neurosis. Successful management of emotional disorders in cardiac and renal disease is indeed complex, taxing the resourcefulness and understanding of the physician.

Summary

As a result of recent advances in our understanding of the pathologic and functional dis-

turbances of the heart in renal disease—that is, acute glomerulonephritis, acute renal failure and chronic renal disease—more rational and effective therapy has been developed. This progress has been reviewed.

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CLINICAL CONFERENCES

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An Unusual Case of Joint Pains and Fever

Berylliosis and Pulmonary Hypertension Mistaken for Rheumatic Fever

By HOWARD B. SPRAGUE, M.D., AND HARRIET L. HARDY, M.D.

DR. SPRAGUE: Dr. Hardy, we are going to discuss this morning the case of our patient, Mrs. George C, whom I first saw in September, 1953 and later referred to you for observation and treatment.

She was a 32 year old married woman who had never been ill prior to February of 1953. Her first baby had been born in September of 1952. In February, for the first time, she began to have redness and swelling of the ankles with considerable pain. This arthralgia migrated to the elbows and to the hands, and she also had pain in the back and shoulders. Her temperature rose to 100.4 F., and she was laid up for about seven weeks. During this time she had some small, red, desquamating nodules over her body, but particularly the arms and legs. She suffered also from shortness of breath, cough, and a tachycardia at a rate of 120 beats per minute. X-ray films of the spine were said to show arthritis. She was treated with bed-rest, oil of wintergreen locally, and sodium salicylate by mouth.

Her cough and dyspnea continued after she got out of bed, and she found herself unable to care for her house and the new baby. There was also extreme fatigue and some sore throat, and she lost 15 to 20 pounds. For a time she was given penicillin by mouth and by inhalation.

When I examined her, she was a thin, ill-appearing, young woman, obviously dyspneic on slight exertion and even at rest, with slight cyanosis. She coughed vigorously on lying down, and it was necessary to examine her in the sitting position. There was no increase in the venous or arterial pulsations in the neck. The heart was not enlarged to percussion. The sounds were of good quality. The pulmonic second sound was louder than the aortic. There were no murmurs. The rhythm was regular at a rate of 100, and her blood pressure was 105/65. I could not make out any dullness of her lungs to percussion, and there were no rales. The liver was not enlarged, and there was no edema of the ankles. There were numerous red, slightly scaly spots over the arms and legs, three or four millimeters in diameter.

Electrocardiogram showed prominent P waves in leads II and III and inverted T wave in lead III and in lead aV_F. There was an RR^1 complex in the precordial lead V_1 with low T waves across the precordium, and inverted in V_1 and V_2 (Fig. 1).

Fluoroscopic examination showed a striking abnormality in the lung fields with an extremely dense mottling throughout both sides. There was no abnormality in the size or the shape of the heart.

With this clue, I investigated her history of industrial exposure more thoroughly. She first said that she had worked as a stenographer, but it appeared on further questioning that in 1943 and 1944, she had worked for a company making fluorescent lamp bulbs and had been exposed to beryllium dust. Radiologic study of the chest (fig. 2) showed the following: "Fluoroscopic examination and films of the chest show diffuse linear nodular densities scattered throughout both lungs from apex to base. The heart is normal in size and shape, and

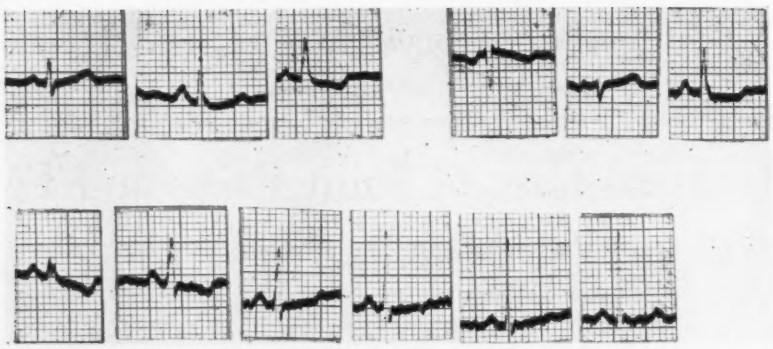

FIG. 1. Electrocardiogram. Top line, leads 1, 2, 3, aV_R, aV_1, aV_F. Bottom line, leads V_1 to V_6.

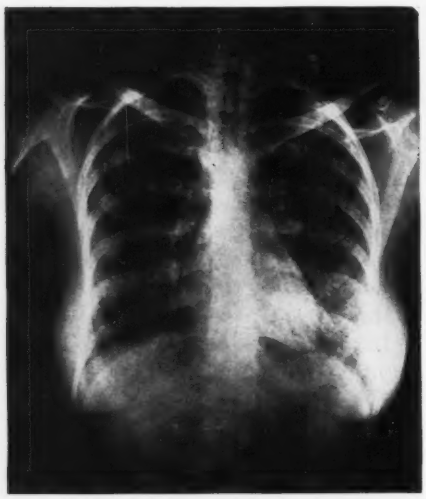

FIG. 2. X-ray, Oct. 6, 1953. Fluoroscopy revealed some limitation of diaphragmatic motion although both leaves moved synchronously. Both lung fields are diffusely studded with small nodular densities. There is increased prominence of both lung roots probably representing some adenopathy. The heart is not enlarged grossly.

the esophagus is normal in position and appearance. No gross enlargement of the mediastinal nodes is present. Conclusion: The diffuse reticulation in both lungs suggests berylliosis. Without the history, Boeck's sarcoid would also be a good possibility, despite the lack of gross hilar adenopathy." Dr. Hardy, would you be good enough to let us know what investigations you undertook when this patient was hospitalized?

DR. HARDY: Because of this particular patient's apprehension about her prognosis, she did not have preliminary pulmonary function studies, as we intend all our cases should. We studied the liver function with the conventional tests and did a variety of biochemical determinations which have been of interest to us, such as blood calcium and phosphorus, and alkaline phosphatase. We also were careful to do tuberculin testing, sedimentation time, and sputum studies, because it is likely we shall one day mistake miliary tuberculosis for beryllium disease.

DR. SPRAGUE: I was particularly interested in bringing out the point here that this woman was considered to have rheumatic fever, and her dyspnea was attributed to rheumatic heart disease. Would you please tell us, Dr. Hardy, about the relationship between the pregnancy and the activation of her beryllium reaction, and also about your experience with joint and skin manifestations of this disease?

DR. HARDY: In our study of cases of chronic beryllium poisoning, we have been impressed and stimulated by the observation that women who have been exposed to beryllium compounds may show no evidence of disease by sign or symptom until a successful pregnancy has been completed. I want to emphasize that the pregnancy, itself, appears, if anything, to be a helpful process, but when the child is 4 to 6 months old the patient may notice inability to gain weight, shortness of breath, and cough, as did Mrs. C.

In answer to your question about experience with joint and skin manifestations of this disease, our observations include another case

with a similar history to Mrs. C. The original diagnosis was rheumatoid arthritis and later proved to be beryllium disease with the joint picture a part of the chemical intoxication. In addition, we have a definite group of patients with mild to moderately severe beryllium poisoning who have intermittent joint pain without x-ray evidence of joint changes or any increase in sedimentation time. These patients' symptoms are relieved with aspirin. Skin manifestations of beryllium effect are divided roughly into three categories: first, the reaction of irritation following direct contact with acid salts of beryllium; second, a subcutaneous granuloma associated in some cases with introduction of beryllium compounds accidentally or, in animals, experimentally; and finally, as in the case of this patient, a small but definite group of cases in which spontaneous skin lesions of great variety simulating Boeck's sarcoid appear as one manifestation of chronic beryllium poisoning (fig. 3).

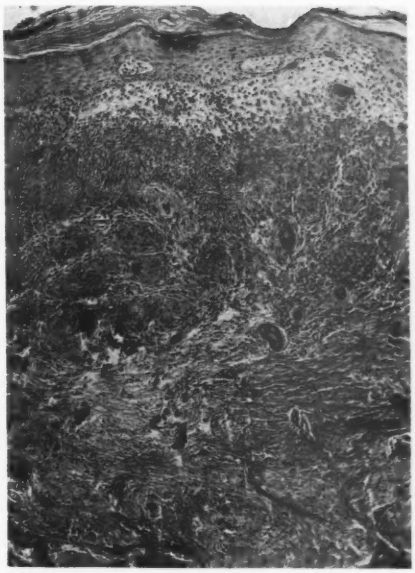

FIG. 3. Pathology: Section from skin biopsy at low magnification (approximately 50×). This demonstrates the diffuse invasion of the corium by fairly well circumscribed granulomas which compress the normal structures of the corium and elevate but do not invade the epithelium. An area is seen in which the granulomas appear fused into a conglomerate group containing a central zone showing early necrosis. The lesions consist of epithelioid cells with scattered lymphocytes and rare, inconspicuous giant cells of the Langhans type. No inclusion bodies or granulocytes are seen. There is moderate fibrosis of the corium.

DR. SPRAGUE: During the time that this patient was in the hospital, the question was again raised as to the significance of the evidence of some degree of right-sided heart strain. How much cor pulmonale have you seen in your patients with beryllium poisoning?

DR. HARDY: Cor pulmonale is a complication in most cases of beryllium disease of any severity. Failure of the right heart is the usual cause of death.

DR. SPRAGUE: You have also explained, Dr. Hardy, that your concept of berylliosis is that it is a completely generalized process. In what other organs and tissues have you found beryllium granuloma or abnormal concentration of beryllium?

DR. HARDY: Beryllium was found at autopsy and biopsy in the lung and also the liver, spleen, kidney; cervical, hilar, and abdominal lymph nodes; bone and skin. The so-called beryllium granuloma, which incidentally we believe is only one part of the pathologic reaction to certain beryllium compounds, has been described in lung, lymph nodes, liver, spleen, kidney and skin.

DR. SPRAGUE: Another point which I should like you to discuss is the relationship between this disease and Boeck's sarcoid. It is my impression that there has been an opinion that sarcoid is commoner in places in the world where the natural concentration of beryllium in the environment is relatively high. Is there anything to support this contention?

DR. HARDY: Dr. Sprague, you are referring to a very interesting but as yet undeveloped observation that the incidence of Boeck's sarcoid can be correlated with the patient's residence in an area where certain soil is found. The original discovery brought out the fact that this particular soil is described as containing small amounts of beryl, the ore from which beryllium comes. However, studies of water, air, and vegetation in these so-called "sarcoid belts" has not borne out the idea that beryllium is present in a detectable concentration. It is

too soon, however, to know whether, with increased knowledge of detection of trace materials in soil, this may or may not be an important lead in the understanding of granulomatous diseases.

DR. SPRAGUE: I have, of course, been immensely pleased at the favorable reaction to cortisone in this case. What is your general experience about the effectiveness of this new therapy? I see that you have cautioned her local physician to have her urine tested once a week for sugar because of the possibility that cortisone might produce glycosuria.

DR. HARDY: We are very much impressed with the effectiveness of cortisone in the management of chronic beryllium poisoning. We do not believe that we are curing the disease although it has been shown in one or two cases by biopsy that the drug has made some change in the granulomata. Klemperer has shown that there is no change in the excretion of beryllium after cortisone therapy. However, if we persist in this form of treatment, our patients are amazingly improved in their general health, an observation which has been checked objectively by pulmonary function studies, showing that there is actual improvement in the oxygen saturation of the blood. We have seen several transient glycosurias in cortisone-treated cases of beryllium poisoning. We have, however, never had to stop treatment for this reason. We have learned that the cortisone must be continued in most cases and medical supervision is required, especially in the presence of infection and when there is any evidence of irritation in the upper intestinal tract.

DR. SPRAGUE: Thank you very much, Dr. Hardy, for discussing these very interesting points. Here, then, is a patient in whose history appear fever, joint pains, and swelling, skin nodules, dyspnea, cough, orthopnea, tachycardia and fatigue. The electrocardiogram suggests some right ventricular strain, and the whole process was originally mistaken for rheumatic fever and rheumatic carditis. The differential diagnosis actually, however, was not difficult because of the negative findings in the heart on auscultation and the characteristic pulmonary pathology on x-ray examination. The delay of almost 10 years in the appearance of beryllium reaction to the level of clinical symptoms is a discouraging fact in the natural history of this disease. It certainly means that all persons thus exposed must continue under medical observation for many years, and the industrial compensation liability is one of indefinite duration. However, there is real hope of successful therapy by cortisone.

ABSTRACTS

BACTERIAL ENDOCARDITIS

Brunson, J. G.: Coronary Embolism in Bacterial Endocarditis. Am. J. Path. **29:** 689 (July), 1953.

The author records the results of his examination of the coronary arteries and the myocardium in nine successive cases of bacterial endocarditis. All but one showed gross scars of varying size, and two of them showed fresh infarctions. Microscopically almost all showed infarcts, old or recent, embolism within small branches of the coronary arteries, and in two cases there were calcific granulomas. None of the vessels showed significant atherosclerosis, and while five of the nine cases showed rheumatic valvular lesions, the author considered the larger scars to be of embolic origin. In one case, Cortisone therapy was associated with striking septic emboli and infarctions. There were no constant or diagnostic changes in the electrocardiogram. Sudden death occurred in five cases.

GOULEY

Parsons, W., Cooper, T., and Scheifley, C.: Anemia in Bacterial Endocarditis. J.A.M.A. **153:** 14(Sept. 5), 1953.

In a series of 200 cases of bacterial endocarditis, anemia was found on initial examination in 150 patients (75 per cent). Anemia was more common than evidence of embolization, splenomegaly, cardiac enlargement, or clubbing of the fingers. Since inadequate antibiotic therapy may temporarily suppress the fever and bacteremia, the association of a cardiac murmur and an unexplained anemia should suggest the possibility of bacterial endocarditis. Occasionally cardiac murmurs may be absent in bacterial endocarditis; therefore the association of an unexplained fever and anemia should also suggest the possibility of this disease.

KITCHELL

Chiles, N. H., Smith, H. L., Christensen, N. A., and Geraci, J. E.: Spontaneous Healing of Subacute Bacterial Endarteritis with Closure of Patent Ductus Arteriosus. Proc. Staff Meet., Mayo Clin. **28:** 520 (Sept. 23), 1953.

Prior to the use of antibiotic and chemotherapeutic agents, spontaneous healing of subacute bacterial endocarditis was rare. The authors report an unusual case in which there occurred spontaneous healing of subacute bacterial endarteritis associated with a patent ductus arteriosus with closure of the ductus. Two courses of treatment with sulfonamides had been tried without avail in this patient. This patient continued to have a rather stormy course for about one and one-half years, accompanied by frequent episodes of chills and fever. After this time, the temperature subsided and his clinical condition improved. The man is now, (15 years later) perfectly well, active and without symptoms. The present-day concept of the treatment of patients with patent ductus arteriosus complicated by bacterial endocarditis is discussed briefly.

SIMON

Donzelot, E., Le Bozec, J. M., Laham, J., and Kaufmann, H.: The Electrocardiogram in Subacute Endocarditis. Acta cardiol. **8:** 465 (Fasc. 5), 1953.

The authors report on serial electrocardiographic investigations in 200 cases of subacute bacterial endocarditis, before, during and after treatment. Frequent findings were left heart strain (70 per cent) and signs of left auricular pathology (40 per cent). Right heart strain, auricular fibrillation and signs of right auricular involvement were relatively rare (1.5 to 5 per cent).

Systematic electrocardiographic studies are important in subacute bacterial endocarditis since alterations of the curve during therapy can be corre-

lated with the course the disease is taking. Evidence of myocardial involvement is seen mostly in cases with negative blood cultures. The presence of such alterations before initiation of treatment does not permit prognostic conclusions. However, when abnormalities like bundle-branch block, A-V block, or, rarely, signs of myocardial infarction occur during penicillin therapy, the outlook of the case becomes poor—regardless of the clinical symptomatology.

PICK

BLOOD COAGULATION

Izzo, P. A., Stevens, R. C., Tomsykoski, A. J., and Rodriguez, C. E.: Hemopericardium Associated with Anticoagulant Therapy. J.A.M.A. Arch. Int. Med. **92:** 350 (Sept.), 1953.

A review of the literature has been made of cases of hemopericardium associated with anticoagulant therapy, and three additional cases are reported, two associated with bishydroxycoumarin and one with ethyl biscoumacetate (Tromexan) therapy. This is the first reported case of hemopericardium associated with ethyl biscoumacetate.

The diagnosis of hemopericardium should be suspected in the presence of (a) recurrent chest pain without renewed electrocardiographic evidence of recent myocardial injury, (b) a prolonged and persistent or recurrent friction rub, (c) circulatory collapse accompanied by a drop in blood pressure, relatively sudden hepatomegaly, and distended neck veins, (d) sudden onset of unexplained anemia and (e) roentgenographic evidence of pericardial effusion.

BERNSTEIN

Beazley, H. L., Foster, W. J., Ory, A. A., and Chapman, D. W.: The Effect of Intravenous and Intramuscular Paritol on the Clotting Time. Am. J. M. Sc. **226:** 275 (Sept.), 1953.

Paritol is a synthetic heparinoid which acts to retard the clotting time of the blood by inhibiting the action of thrombin. Its effects were studied using animals and humans by measurement of the clotting time and prothrombin time. Single injections of the agents in several stages of purity produced prolongation of the clotting times for periods of 8 to 10 hours; therapeutic levels could be maintained by repeated injections. A slight effect upon the prothrombin time was observed. The more purified preparations caused minimal local reactions when given intramuscularly. With intravenous administration, they caused numbness and tingling of the fingers and toes; occasional transient hypotensive responses were observed. Paritol produced a rise in the blood urea nitrogen; in patients with renal disease, the urea retention was marked. Protamine sulfate was found to be an effective antidote for Paritol administration. The authors feel that the usefulness of Paritol is limited because of toxic reactions.

SHUMAN

Utz, J. P., Mann, F. D., and Barker, N. W.: Clearing of Lipemic Plasma by Heparin. Proc. Staff Meet., Mayo Clin. **28:** 531 (Sept. 23), 1953.

Studies are reported of the clearing effect of intravenous heparin on lipemic plasma induced after a fatty meal in a total of 69 atherosclerotic and control patients. In 11 of 12 patients who received a dose of 3 mg. of heparin, the clearing of the plasma did not persist for one hour. When the dose of heparin was increased to 20 mg. the clearing effect failed to persist for two hours in all 10 patients who were tested. When heparin and the fatty meal were given simultaneously in 11 patients, no detectable difference was noted in the average degree of lipemia three hours later. The intravenous injection of 100 mg. of heparin per day for three days changed the response toward normal in four atherosclerotic patients. A similar effect was not noted in three atherosclerotic patients who did not receive heparin between tests.

SIMON

Simon, E. P., and Wright, I. S.: Controlled Ergometric Studies of Effect of Heparin on Intermittent Claudication. J.A.M.A. **153:** 98 (Sept. 12), 1953.

The authors utilized an electrically driven and controlled treadmill ergometer to study the effect of heparin on intermittent claudication of six patients with arteriosclerosis obliterans. Marked variability in claudication time was noted in the same patient. No beneficial effects were noted after 4 to 14 weeks of treatment with heparin.

ABRAMSON

Grüner, A., Hilden, K., and Hilden, T.: The Effect of Heparin and Protamine Sulphate on the Occurrence of Chylomicrons in Human Blood. Scandinav. J. Clin. & Lab. Invest. **5:** 241 (No. 3), 1953.

The effect of heparin on the number of chylomicrons in the blood after ingestion of 150 ml. of a 13 per cent cream, was observed in four young and four old subjects. When 150 mg. of heparin was given intravenously two and one-half hours after ingestion of fat, the postalimentary chylomicronemia was considerably reduced in both groups. An intravenous injection of 150 mg. of heparin simultaneously with ingestion of fat prevented the postalimentary chylomicronemia. Doses of heparin down to as little as 1.2 mg. had a definite effect, but less than 1 mg. had a doubtful effect. Intramuscular doses of 50 mg. produced a moderate effect, but doses of 20 mg. were ineffective. Sublingual administration of 100 mg. of heparin simultaneously with ingestion of fat failed to produce appreciable effect.

It was found that protamine sulfate is able to obviate the heparin effect almost completely. It was also observed that protamine sulfate increases the spontaneous number of chylomicrons in fasting individuals.

ROSENBAUM

CONGENITAL ANOMALIES

Ingalls, T. H., and Purshottam, N.: Fetal Risks from Rubella during Pregnancy. New England J. Med. **249:** 454 (Sept. 10), 1953.

This study is concerned with the review of 19 cases, reported to the editors of this journal following a request one year earlier that physicians practicing obstetrics submit certain basic data concerning rubella contracted during pregnancy. The study of these 19 cases disclosed that when rubella occurred during the first trimester of pregnancy there was a risk of losing the conceptus in less than 10 per cent and a risk of a defective infant in 7 per cent of the cases. When rubella occurred in the second trimester there were 7 per cent stillbirths and 6 per cent defective infants. When pooled with the observations of other observers, the total risk of stillbirth or deformity was 17 per cent when rubella occurred in the first trimester of pregnancy, and 12 per cent when the infection complicated the second trimester.

ROSENBAUM

O'Sullivan, W., and Steinberg, I.: Coarctation of the Aorta. Bull. New York Acad. Med. **29:** 68 (Sept.), 1953.

Unless there is a serious contraindication coarctation of the aorta should be repaired surgically. The simplest and safest method of operative repair in most patients is resection with direct end-to-end anastomosis. If the stenotic area is too long or the adjacent aorta too diseased, the use of a graft may be necessary. The authors report a series of 23 patients subjected to operation. In three no repair was performed. Nineteen of the patients had a resection of the aortic obstruction and an end-to-end anastomosis. The other patient had a long atresia of the aorta, and the splenic artery was employed as a shunt around the obstruction. The one operative fatality resulted from cardiac arrest which appeared shortly after the removal of the aortic clamps. The postoperative complications consisted of one case of homologous serum jaundice, one transient radial nerve palsy, two paralyses of the left vocal cord, and one case of brain abscess. The short-term results of pre- and postoperative blood pressure was good.

SAGALL

Chapman, C. B., and Fraser, R.: Clinical and Hemodynamic Features of Uncomplicated Interatrial Defect in Adults. Am. Heart J. **46:** 352 (Sept.) 1953.

Nineteen adult patients, 10 men and 9 women of ages ranging from 17 to 51, were studied with respect to clinical and hemodynamic features of their interatrial defects by means of cardiac catheterization. The pulmonary arterial flow was often markedly increased but may be only slightly so. Slight to moderate pulmonary hypertension is a frequent finding and severe elevation rare. No apparent relation was found between flow and pressure in the pulmonary arterial system. Right ventricular pressure work is increased usually. Prominent systolic murmurs, usually basal, are frequent and may be accompanied by a thrill. The frontal plane QRS vector is usually +90 degrees or more where the interatrial defect is significant.

RINZLER

Holswade, G. R., and Goldberg, A. P.: Patent Ductus Arteriosus. Bull. New York Acad. Med. **29:** 694 (Sept.), 1953.

The authors review the historical facts concerning operative repair of patent ductus arteriosus and the present means of diagnosis. Their operative series consisted of 22 females and 14 males, mainly children or adolescents. In 34 the ductus was closed using the suture-ligature technic. In 14 cases there were no murmurs after operation. Thirteen patients had persistent pulmonic systolic murmurs. In all cases, excepting one in whom there was evidence of recanalization, the results are considered to be good and the patients are leading normal lives. There were three complications and no deaths in the series. In two patients with reversal of the flow in a large ductus, exploration was carried out, but permanent interruption of flow through the ductus was not carried out.

SAGALL

Cosh, J. A.: Patent Ductus Arteriosus with Pulmonary Hypertension. Brit. Heart J. **15:** 123 (Oct.), 1953.

Three instances of patent ductus arteriosus complicated by severe pulmonary hypertension are presented.

The author believes that pulmonary hypertension is unrelated to the patent ductus and that the ductus should not be ligated if the pulmonary pressure is higher than the aortic. The diagnosis is difficult because (1) the characteristic murmur is replaced by a systolic pulmonic murmur and (2) cyanosis, greater in the lower limbs than in the upper, occurs only in the severer cases with a reversed shunt. Cardiac catheterization and angiocardiography may be necessary for diagnosis, and even these methods may fail if the pulmonary and aortic murmurs are nearly equal.

SOLOFF

Record, R. G., and McKeown, T.: Observations Relating to the Etiology of Patent Ductus Arteriosus. Brit. Heart J. **15**: 376 (Oct.), 1953.

The authors report on observations, primarily environmental, possibly relating to the etiology of patent ductus arteriosus occurring in 166 instances. The mortality was lower and the instances of affected males higher in the first born of those with a higher maternal age. This observation is attributed to the better social status of the parents. There was a seasonal fluctuation in the incidence of affected females but this fluctuation was not attributable to rubella. A history of fetal distress was very common and occurred in 43 or 28 per cent of the affected individuals. This positive history is regarded as very significant. The incidence of congenital heart disease in younger siblings was higher than that of the normal population.

SOLOFF

McCullough, A. W.: Further Examples of Endocardial Cushion Defect in Production of a Cardiac Anomaly Complex. J. Pediat. **43**: 429 (Oct.), 1953.

The author describes anatomically and discusses three cases of an anomaly complex of the heart consisting primarily of (1) patency of the interventricular septum in the region of the roots of the great vessels, and (2) transposition or other anomalies of the great vessels external to the heart. It is posited that this anomaly complex results from a failure of or delay in endocardial cushion development during the period of *septation*, that is, from the fourth to the seventh fetal week.

MAXWELL

CONGESTIVE HEART FAILURE

Friedberg, C. K., Taymor, R., Miner, J. B., and Halpern, M.: The Use of Diamox, a Carbonic Anhydrase Inhibitor, as an Oral Diuretic in Patients with Congestive Heart Failure. New England J. Med. **248**: 883 (May 21), 1953.

Inhibition of carbonic anhydrase activity in renal tubule cells has been found to diminish the retention of sodium as well as impairing the tubular secretion of hydrogen ion. The sulfonamides have been found to be carbonic anhydrase inhibitors and one of the most active of these is 2-acetylamino-1,3,4,-thiadazole-5-sulfonamide, known commercially as Diamox. The effect of this material was studied in 26 patients.

When administered intravenously increased water and sodium excretion appeared 30 minutes earlier than when the drug was given orally. All but three patients showed an increased 24-hour urine volume after oral administration of Diamox. The rate of sodium excretion increased in all subjects after Diamox regardless of the diuretic response with an average of 90 mEq. per 24 hours in those with a satisfactory diuresis and a mean increase of 30 mEq. in those with diuresis insufficient to control heart failure. Excretion of potassium increased in all patients after Diamox, but there was no correlation between changes in potassium excretion and clinical response. The effect of Diamox on chloride excretion was variable. When the drug was given in doses of 0.25 Gm. every eight hours for three or more days, there was a gradual diminution of its effect upon the excretion of water, sodium and potassium. It was found necessary to discontinue the drug for at least 48 hours before a renewed response could be elicited. When given in doses of 0.25 Gm. once daily no diminution in effect was observed. The most advantageous dosage schedule seemed to be 0.25 Gm. three times daily for two days, with courses repeated every two to seven days or continuous administration of 0.25 Gm. once daily. No serious toxic manifestations occurred. Mild drowsiness occurred in six patients and four had mild tingling of the fingers. No evidence of renal or hemopoietic disturbance was observed. It was felt that in 18 patients the diuresis, weight loss and clinical improvement which followed the oral administration of Diamox compared favorably with those after a mercurial diuretic given parenterally.

ROSENBAUM

Burdette, W. J.: Exposure of Human Cardiac Muscle to Radioactive Digitoxin in Vitro. Am. Heart J. **46**: 602 (Oct.), 1953.

Slices of human cardiac muscle obtained by biopsy at the time of exploratory thoracotomy were incubated with C^{14}-labeled digitoxin, in Warburg vessels. The activity of barium carbonate, which was recovered from carbon dioxide dissolved in potassium hydroxide in the center well of the vessels, was determined with a thin-window Geiger-Mueller tube and also a flow counter. No radioactivity was detected in the samples even though the slices respired at increased rate in the presence of glycoside. This suggests that digitoxin acts catalytically without conversion to $C^{14}O_2$ by the tissue.

RINZLER

CORONARY ARTERY DISEASE

Papacharalampous, N., and Zollinger, H. U.: Morphology and Pathogenesis of Subtotal and Total Coronary Occlusion. Schweiz. med. Wchnschr. **83**: 895 (Sept.), 1953.

The various mechanisms leading to partial or complete occlusion of a coronary artery were studied in serial histologic sections of excised coronary arteries in 126 cases who died from recent myocardial infarction. In 11.1 per cent there was only intramural bleeding due to arteriosclerosis, and in 16.7 per cent the same process was accompanied by secondary thrombosis. Pure arteriosclerotic vascular occlusion was found in 25.8 per cent and arteriosclerotic stenosis with subsequent thrombosis in 37.7

per cent. In 8.8 per cent the presence of primary inflammatory lesions (coronaritis) was established, with or without secondary coronary thrombosis.

The findings were further analyzed with respect to the age and sex of the patients, their relationship to generalized arteriosclerosis, the pathogenesis of actual occlusion, and the localization of the resulting myocardial infarction. The significance of these anatomic findings, particularly that of intramural vascular bleeding, is discussed with respect to the therapeutic use of anticoagulants. It would appear that the beneficial effects of anticoagulant therapy dominate over its potential dangers.

PICK

Levine, H. D.: Non-Specificity of the Electrocardiogram Associated With Coronary Artery Disease. Am. J. Med. **15**: 344 (Sept.), 1953.

Changes in the T wave, RS-T segment, and QRS complex of the electrocardiogram generally reflect myocardial ischemia, current of injury, or death of muscle, respectively. The T wave, the most labile and least specific feature of the electrocardiogram, may be affected by a great variety of factors, only one of which is ischemia. Changes in the RS-T segment usually, but not always, correspond to acute muscle damage. It is generally transitory and rarely permanent. Like the T wave, this may indicate an anatomic or a biochemical lesion. QRS changes practically always signify death or replacement of heart muscle; this is generally associated with coronary artery disease. Rarely it may result from heart muscle damage from other causes. The electrocardiogram is quite accurate in the detection of acute myocardial infarction but inaccurate in the diagnosis of old or of multiple infarcts. It remains to be seen whether the newer vectorcardiography will attain a greater accuracy.

HARRIS

Kennamer, R., Bernstein, J. L., Maxwell, M. H., Prinzmetal, M., and Shaw, C. M.: Studies on the Mechanism of Ventricular Activity. V. Intramural Depolarization Potentials in the Normal Heart with a Consideration of Currents of Injury in Coronary Artery Disease. Am. Heart J. **46**: 379 (Sept.), 1953.

This investigation deals with intraventricular potentials during normal sinus rhythm registered by means of a specially designed electrode located at various depths within the ventricular wall, the interventricular septum, and the papillary muscle of 32 dogs. A series of experiments was performed which established (a) that the presence of the plunge electrode in the myocardium did not alter the normal course of depolarization, and (b) that the depolarization complexes registered by the plunge electrode represented essentially local potentials.

Pure QS or rS waves were recorded throughout at least the innermost two-thirds of the intramural myocardium in both ventricles as well as from all levels of the left papillary muscle. Intraseptal leads also exhibited essentially negative deflections, although considerable positivity was noted in the center and right side of the septum. Only the epicardial surface and a thin subjacent layer of the walls yielded predominantly positive depolarization complexes. In general, negative potentials were found to predominate in roughly 80 per cent of the musculature during ventricular depolarization, while about 20 per cent of the myocardium was predominantly positive. This observation indicates that the ventricular wall does not depolarize in the same manner as do the auricles.

Pure QS waves consistently were obtained throughout the left ventricular cavity as well as from all portions of the right ventricular cavity except in the immediate vicinity of the septum. Cavity leads recorded near the right septal surface occasionally displayed a small R wave derived from the initial positivity of the right septal surface.

The velocity of the depolarization wave was measured in 20 animals by timing the onset of the downstrokes in intramural leads from multiple depths of the left ventricular wall. As determined by this method, the rate of depolarization appears to be considerably more rapid in the innermost two-thirds of the wall than in the superficial layers.

Currents of injury, manifested by RS-T segment elevation, always occurred for a brief period following the introduction of the plunge electrode into the myocardium. The RS-T segment deviation was markedly less in subendocardial leads than in subepicardial leads, indicating that subepicardial muscle characteristically is capable of producing more intense injury currents than are the deeper layers of the myocardium.

The observed weakness of subendocardial injury currents in experimental animals suggests that the downward RS-T segment deviation, which is seen clinically in angina pectoris, is not attributable to subendocardial anoxia, as is generally believed. On the basis of the same experimental observation, a new theory concerning the cause of RS-T segment elevation following coronary occlusion is proposed which appears to reconcile apparent discrepancies among the electrocardiographic, anatomic, and pathologic findings. When a coronary artery is occluded, the entire subendocardial region, including the muscle surrounding the ventricular cavity, undergoes at least as severe anoxia as the overlying subepicardium. Nevertheless, as in the experiments, the subendocardial muscle experiences a less drastic impairment of polarization (and depolarization) than the subepicardial muscle, causing a potential difference between the two regions. Under such circumstances, current flows in the same direction as in primarily subepicardial injury, and the precordial electrode

registers an upwardly displaced RS-T segment, since it faces the positive side of the dipole. Thus the direction of RS-T segment displacement following coronary occlusion may be related to functional, rather than anatomic or pathologic, differences between the various layers of the ventricular wall.

RINZLER

Fabre, H., and Linquette, Y.: Tobacco and Coronaries. Arch. mal. coeur **46**: 898 (Oct.), 1953.

Twenty-nine anesthetized dogs were subjected to inhalation of cigarette smoke at a tempo used by an ordinary smoker. In 10 of the dogs a branch of a coronary artery had been ligated prior to the experiment. Electrocardiograms were recorded during inhalation and afterwards until electrocardiographic alterations disappeared. These experimental data were then compared with human tracings obtained in nonsmokers following smoking of two cigarettes, and in habitual cigarette smokers following the smoking of a cigar.

The results were inconsistent in the animal as well as in the human group. Whereas in some tracings (including some abnormal tracings produced in dogs by coronary ligation) no alteration occurred after smoking, others revealed profound transient alterations consisting in depression of the S-T segment and/or inversion of T waves. In view of this variation of results the authors conclude that an abnormal electrocardiographic response to smoking depends largely on individual susceptibility. This varies in man as well as in the animal from case to case.

PICK

Oliver, M. F., and Boyd, G. S.: The Plasma Lipids in Coronary Artery Disease. Brit. Heart J. **15**: 387 (Oct.), 1953.

The plasma lipids were determined in 200 individuals with coronary artery disease and in 200 controls. Although there is individual overlapping, there was significant elevation of the plasma total cholesterol and plasma total-cholesterol/phospholipid ratio in all decades in the coronary artery disease group. Maximal elevation occurred in the earliest decade of the study in men with coronary artery disease. In the sixth decade in women, the value for the control group rose to the coronary artery group level.

SOLOFF

James, T. N., and Drake, E. H.: Cryoglobulins in Coronary Artery Disease. New England J. Med. **249**: 601 (Oct. 8), 1953.

The descriptive term "cryoglobulin" has been applied to substances in serum which precipitate when the serum is exposed to cold temperature. The authors studied 69 patients with coronary-artery disease in regard to the presence of cryoglobulinemia. Four patients had severe angina and 65 had had a recent myocardial infarction. In 40.6 per cent of these patients small amounts of cold-precipitable substances were found in the serum. There was no correlation between cryoglobulinemia and high titers of cold agglutinins, positive dilution–turbidity tests, elevated blood cholesterol or sedimentation rate. Seven serums with negative cryoglobulin tests and nine with positive tests showed a normal viscosity at both 5 C. and 37 C. These findings make it unwise at the present time to attach any significance to the presence of small amounts of cold-precipitable substances in the serum of patients with coronary-artery disease.

SAGALL

Sonnet, J., and Sibille, A.: Electrophoresis of Blood Proteins in Myocardial Infarction. Acta cardiol. **8**: 479 (Fasc. 5), 1953.

In 35 cases of myocardial infarction, the authors used paper electrophoresis to study the inflammatory reaction of blood proteins to tissue necrosis. Within the first months subsequent to acute coronary occlusion, an increase of α_2 globulins was found in 21 out of 23 analyses. In this first stage of the disease the intensity of the reaction is of no value for the prognosis and appears to be independent of the localization and extent of the infarcted area. When the disease takes an uneventful course the curve of α_2 globulins returns to normal levels within the second month. In four cases with unexpected fatal outcome the curve reached a second peak two months after the attack.

PICK

Bourgain, R., and Gerbaux, A.: Electrokymographic Study of Left Ventricular Ejection Delay in Myocardial Infarction. Acta cardiol. **8**: 519, (Fasc. 5), 1953.

The authors study the electrokymogram of the left ventricle after severe myocardial infarction with incomplete recovery. Incomplete recovery was admitted when a systolic expansion recorded by the electrokymogram revealed severe damage to the wall of the ventricle, or there was the clinical picture of heart failure.

Nineteen cases presented systolic expansion and no evidence of failure, while six others presented evidence of failure.

In the great majority of cases (19 in all), the tracing of the aortic arch, compared with the electrocardiogram, revealed a delay of ejection which exceeded 0.15 second, this being the highest delay still within normal limits.

According to Seghers and Hendricks, the ejection delay of left bundle-branch block would be mainly due to the conditions of the myocardium and not to the block itself. The present study seems to confirm their views by proving severe delay even without excessive broadening of QRS.

LUISADA

Davis, F. W., Jr., Scarborough, W. R., Mason, R. E., Singewald, M. L., and Baker, B. M. Jr.: The Effects of Exercise and Smoking on the Electrocardiograms and Ballistocardiograms of Normal Subjects and Patients with Coronary Artery Disease. Am. Heart J. **46:** 529 (Oct.), 1953.

The high incidence of abnormal ballistocardiograms in older "normal" persons over the age of 50, and the relative frequency of normal records in those under 50 who have clinical evidence of coronary artery disease limit the diagnostic value of the resting ballistocardiogram for coronary atherosclerosis. The authors investigated "stress-eliciting" procedures, namely exercise and cigarette smoking, in 200 subjects to distinguish the clinically normal person from the patient with angina pectoris and/or remote myocardial infarction. The ballistocardiogram in 7.9 per cent of normal control subjects and in 31.4 per cent of patients with coronary artery disease deteriorated after exercise. The electrocardiographic response to exercise was positive by Master's criteria in 22.8 per cent of normal controls, and in 50 per cent of the subjects with angina pectoris or remote myocardial infarction. The ballistocardiogram in 6.8 per cent of normal control subjects and in 58.6 per cent of patients with coronary artery disease deteriorated after smoking a cigarette. This meant that the diagnostic margin between diseased persons and normal controls was 4:1 by the ballistocardiograph after stress, 2:1 by the electrocardiograph after stress and 9:1 by the cigarette test.

The authors however state that it is not their purpose to suggest the routine use of the cigarette test as a diagnostic procedure in patients, but rather to encourage further investigation of the effects of smoking and nicotine on the cardiovascular functions as studied by analysis of the form of the ballistocardiogram.

RINZLER

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY AND BALLISTOCARDIOGRAPHY

Helm, R. A., and Iglauer, A.: A Statistical Comparison of Normal Ballistocardiograms Recorded with a High-Frequency Table and with Various Instruments which Record Body Motion Directly. Am. Heart J. **46:** 321 (Sept.), 1953.

Normal ballistocardiograms recorded with a high-frequency table were compared with tracings taken simultaneously for each of three types of instruments which record the movement of a cross-bar placed across the shins. These instruments were photoelectric, piezoelectric, and an electromagnetic ballistocardiograph. Statistically, a high degree of correlation was found between the IJ and JK segments recorded with the table and the corresponding segments simultaneously recorded with each of the instruments studied. No significant correlations were found in individual subjects in the case of the JK:IJ ratio. The variation between the means of the JK:IJ ratio recorded in each of 10 subjects with the three instruments was not significantly different from the variation of the means of corresponding ratios recorded simultaneously with the table. The reproducibility of repeated tracings obtained with the instruments which record body motion directly was in general inferior to the reproducibility of tracings obtained with the table. This finding was particularly significant in the case of the photoelectric instrument.

RINZLER

Pierce, J. R., Christianson, L., and Walker, R. P.: Time Relationships of Ballistocardiographic Movements. Am. Heart J. **46:** 329 (Sept.), 1953.

Studies were made on the direct displacement ballistocardiograms of 84 of 90 young healthy medical students and student nurses. The data included time relationships between the ballistocardiographic waves, heart sounds, electrocardiograms, and the carotid and jugular pulses. The following relations were found: (1) a wide variation in temporal relations of the H peak; (2) a close temporal correlation between: (A) the K nadir and the second heart sound; (B) the L peak and the carotid incisura; and (C) the N peak and the jugular V peak; (3) an inverse relationship between the K-N time and the heart rate; (4) the occurrence of one or more waves during the period of diastasis; (5) a wide pattern variation of the G-H upstroke; and (6) a temporal relationship of the G-H upstroke to both the presystolic and isometric contraction phases of the cardiac cycle.

RINZLER

Metianu, C., Durand, M., and Danzier, G.: The Electrocardiogram in Coarctation of the Aorta. Cardiologia **23:** 274 (Fasc. 5), 1953.

Among 44 cases of coarctation of the aorta, in ages 8 to 39 years, the electrocardiogram was normal in 6 (13.5 per cent) and revealed left ventricular strain in 36 (82 per cent). In 11 cases the latter was associated with left bundle-branch block, and in seven with right bundle-branch block. In two cases isolated complete right bundle-branch block was present. Left axis deviation is found more frequently in cases with an additional aortic valvular lesion (suggested by a diastolic murmur). No correlation could be established between electrocardiographic findings and the degree of stenosis or the height of the blood pressure. The finding of electrocardiographic alterations in a younger person with coarctation is an indication for immediate surgery, while in older persons such findings represent a contraindication in view of the possibility of higher risks involved.

PICK

Corsi, V., San Giorgi, M., and Corelli, D.: Contribution to the Electrocardiographic Localization of Auricular Myocardial Damage. Cardiologia **23:** 255 (Fasc. 5), 1953.

The author investigated changes of the electrocardiogram which were produced by cauterization, or application of a caustic solution to the atria of dogs. The main alterations thus produced consisted in a positive or negative displacement of the P-R segment and were due to injury currents affecting atria repolarization (Ta wave). The polarity of displacement which differed in various leads, depends on the direction of the axis of a particular lead relative to the location of the injury. Thus, necrotic lesions of the posterior wall of the right atrium produced downwards deviation of the P-Q segment in leads II, III, aV_F, in left precordial leads and leads from the atrial cavity, whereas upward displacement was recorded in aV_R, aV_L, in esophageal, epicardial and right precordial leads. Lesions of the left atrium generally produced P-Q deviations opposite in direction to those seen in right atrial lesions. A lesion of the right atrial wall, even if limited in size, almost invariably causes disturbances of cardiac rhythm (different types of A-V block, A-V dissociation and ectopic tachycardias including auricular flutter and fibrillation). Only exceptionally do such disorders develop as a result of damage to the left atrium.

From the clinical standpoint right precordial leads appear most valuable for the study of atrial lesions, since the atrial potentials recorded in these leads closely resemble those of direct epicardial leads.

PICK

Taran, L. M., and Szilagyi, N.: The Range of the Measured Q-T Interval. Bull. St. Francis San. **10:** 36 (Oct.), 1953.

The wide scatter of values for the measured Q-T interval and the obvious overlapping of these values in electrocardiograms of patients with marked differences in cardiac status would seem to throw doubt upon the value of the measurement in assessing the integrity of the heart muscle. On the other hand, the great stability of the measurement of the Q-Tc and its sensitivity as an index of the degree of carditis has been well established provided that the Q-Tc is calculated on the basis of averages derived from many cycles and several leads. This points up the well known physiologic principle that the cardiodynamic events as expressed in an individual cardiac cycle at a given moment do not mirror the total functional integrity of the heart. In normal hearts sinus arrhythmia, for example, there are short runs in which the heart action is rapid, followed by long runs of slow cardiac action. While the scatter of values in such an instance would be wide, the average value would be weighted by the long cycles. This average value is representative of the average cardiac functional activity. In patients with acute carditis, the scatter of Q-T values may be sufficiently wide to fall within the area of scatter of the normal group. In this instance, however, the average value is weighted by the greater number of cycles with long Q-T intervals in respect to the RR. The total functional activity here is represented by the long Q-Tc. Obviously, to differentiate between the functional integrity of the heart in health and disease, values which overlap and which are found in the scatter areas are representative. Thus, to obtain a true differentiation, enough cycles must be measured and averaged to represent the various phases of cardiac activity; however, emphasis in each case will be in the direction of the most dominant phase of cardiac activity.

BERNSTEIN

Kessel, I.: The Electrocardiogram on the First Day of Life. Brit. Heart J. **15:** 430 (Oct.), 1953.

The author reports the electrocardiographic pattern in 15 Bantu infants less than one day old. All had sinus rhythm, electrically vertical hearts and large Rv_1. The transition zone in the precordial leads tends to occur between V_3 and V_4. A large R wave was always present in the right-sided chest leads. In two cases, an upright T wave became negative on passing from the right side of the chest to the left, and once a negative T wave on the right side became positive on passing to the left.

SOLOFF

ENDOCRINE EFFECTS ON CIRCULATION

Grad, Bernard: Changes in Oxygen Consumption and Heart Rate of Rats during Growth and Ageing: Role of the Thyroid Gland. Am. J. Physiol. **174:** 481 (Sept.), 1953.

Oxygen use and heart rate are low at birth, climb during the first month and decline to old age. Thyroidectomy produces a greater percentage fall in these parameters in the young with the result that the decline is not seen. Older animals are less responsive to thyroxine. A rat at 3 weeks uses less oxygen than at 2 weeks even though the former weighs more. Male rats have a higher oxygen use than females. If corrected for size males have faster rates. Stroke volume increases with growth. There is little change in A-V oxygen differences.

OPPENHEIMER

Sevy, R. W., and Ohler, E. A.: Effect of Renin on Adrenal Ascorbic Acid Concentration in Rats. Am. J. Physiol. **174:** 471 (Sept.), 1953.

Depletion of adrenal ascorbic acid obtained after intravenous injection of renin, was not present in rats deprived of their hypophyses. This decrease in

ascorbic acid was not obtained if the renin was inactivated by heat. Antirenin from dog serum completely blocks the effect of renin. Dibenzyline (adrenergic blocking agent) only partly prevents the action of renin.

OPPENHEIMER

HYPERTENSION

Zimmerman, I. J., Berion, R. E., and MacMahon, H. E.: Pheochromocytoma of the Urinary Bladder. New England J. Med. **249:** 25 (July 2), 1953.

What is believed to be the first instance of pheochromocytoma of the urinary bladder is reported from a woman aged 74 years. The tumor was an invasive one, yet there were no mitoses nor signs of cellular dissociation. The tumor is believed to have arisen from paraganglionic tissue such as may occur in the adventitia and wall of the bladder. A review of the history after the nature of the tumor was learned, revealed that the patient had noted attacks of tachycardia and flushing of the face for three years prior to operation. Furthermore, rapid beating of the heart had frequently accompanied emptying of the bladder. These symptoms cleared after the operation.

ROSENBAUM

Hilker, R. R., Rhoads, P. S., and Billings, C. E.: Clinical Use of Hydralazine and Hexamethonium in Treatment of Hypertension. J.A.M.A. **153:** 5 (Sept. 5), 1953.

The ranges and falls of pressures in 50 patients given hydralazine, 15 patients using hexamethonium and 14 using a combination of both hydralazine and hexamethonium are reported. The authors felt there was no way of predicting which patients would respond to therapy. Four patients who previously had had sympathectomies were treated, and their response was no different from that of other patients. All patients with a presumed renal hypertension responded well. Hydralazine hydrochloride is a safe, moderately effective, hypotensive drug which can be given to office patients. The incidence of toxic effects is high but these are transient. Hexamethonium is a powerful, dangerous, antihypertensive drug whose oral use results in unpredictable wide variations in blood pressure. It is not safe to start office patients on this therapy. Its main effect is brought about through postural hypotension. The use of this drug should be restricted to severe hypertension that does not respond to other measures. Combined use of these drugs results in only slight advantage. The authors feel these drugs should be used with caution in elderly and severely arteriosclerotic patients. Although these drugs are the best now available, they are not a completely satisfactory treatment for hypertension.

KITCHELL

Palmer, R. S., and Muench, H.: Course and Prognosis of Essential Hypertension. J.A.M.A. **153:** 1 (Sept. 5), 1953.

This is a report on the survival of 453 patients with different degrees of essential hypertension. They were first seen and classified more than 10 years ago and were recently subjected to intensive follow-up. In the classification, grade I included persons with minimal organic change in the three vital areas of head, heart and kidneys; grade II those with definite or marked change but no functional impairment; grade III those with organic change and functional impairment; and grade IV those with papilledema. The same series of cases was reported four years ago and six years ago. The treatment in these cases was chiefly dietary together with mild sedation and sometimes potassium sulfocyanate. These patients are considered valid controls with the results of surgical treatment or with those of any single medical treatment consistently followed. It is felt that because of the inevitable loss of patients from observation the mortality rates as given may be somewhat exaggerated. Several tentative conclusions are made: (1) relative risk is highest in the young and decreases rapidly with age; (2) mortality in women is lower (except for those in grade IV) and increase of severity is slower; (3) average age increases from grade I to grade III; (4) duration of disease apart from advancing age does not seem to have any effect on mortality, except in grade IV; (5) survival rates relative to those of the general population follow simple patterns that may be expressed mathematically; and (6) with each increase in grade, patients die at a faster rate than that expected in the population at large, but this increase in mortality tends to diminish with time under observation or higher ages.

KITCHELL

Gill, R. J., Duncan, G. G., and Reinhardt, D. J.: Arterial Hypertension; The Therapeutic Effect of Sodium Restriction Combined with 1-Hydrazinophthalazine or Dibenzyline. Am. J. M. Sc. **226:** 249 (Sept.), 1953.

Basing their evaluation of therapeutic effects upon the percentage drop in the blood pressure of hypertensive patients, the authors found that the dietary sodium restriction and cation exchange resins combined with Apresoline exerted a beneficial effect. These results measured as reduction of blood pressure; improvement in cardiovascular and renal function were not observed when each of these agents were used alone. Side effects noted in certain patients included tachycardia, sensations of fatigue, giddiness, headache, and a maculopapular rash. Dibenzyline was of little value as a hypotensive agent when employed alone. Combined with low sodium cation exchange resin therapy, the blood pressure responses with this agent were quite vari-

able and fluctuating. Undesirable side effects included miosis with visual blurring, dizziness, muscular aching, weakness, headache and tachycardia. The authors emphasize the need for vigilance in keeping the patients on their low sodium diets when treatment with these drugs is undertaken.

SHUMAN

Hall, C. E., and Hall, O.: Reversal of Parabiotic Hypertension Following Separation of the Pairs. Am. J. Physiol. **174:** 401 (Sept.), 1953.

One of the pair in parabiotic rats often develops spontaneous hypertensive cardiovascular disease. Blood pressure returns to normal when the hypertensive rat is separated from the normotensive one.

OPPENHEIMER

Kubicek, W. G., Kottke, F. J., Laker, D. J., and Visscher, M. B.: Renal Function During Arterial Hypertension Produced by Chronic Splanchnic Nerve Stimulation in the Dog. Am. J. Physiol. **174:** 397 (Sept.), 1953.

Although splanchnic nerve stimulation was continued for two to three weeks, blood pressure was increased only during stimulation. During this time the heart rate was not increased. In some of the animals, there was an increase in renal plasma flow, glomerular filtration rate and filtration fraction. However, these changes were not statistically significant. The majority of the dogs showed enough renal vasoconstriction to keep blood flow through the kidney at constant values. The opinion is expressed that splanchnic vasoconstriction was the probable cause of the hypertension.

OPPENHEIMER

Miles, B. E., and DeWardener, H. E.: Effect of Emotion on Renal Function in Normotensive and Hypertensive Women. Lancet **2:** 539 (Sept. 12), 1953.

The present paper records, in hypertensive and normotensive women, the emotional effects on renal function of passing a catheter. Pronounced osmotic diuresis (diuresis attributable to increased excretion of sodium and chloride) was evoked in these patients. In two there was an associated water diuresis.

Of the 10 normotensive women, nine had small osmotic diureses and one of these, a pronounced water diuresis. Evidence is reviewed that the increased salt excretion is more likely to have been due to diminished tubular reabsorption than to associated increase in glomerular filtration rate. The authors suggest that emotional effects may have been responsible for abnormally high rates of salt excretion reported previously in certain circumstances in catheterized hypertensives.

MCKUSICK

Assali, N. S., Clark, L. C., Jr., and Sobel, E. H.: Studies on Toxemia of Pregnancy: Effect of Desoxycorticosterone Acetate (DCA) on Hemodynamics and Electrolyte Balance of Normal Pregnant Women. J. Clin. Endocrinol. **13:** 1030 (Sept.), 1953.

The effects of the intramuscular administration of 10 to 30 mg. of desoxycorticosterone acetate (DCA) daily for three to four days on five women in the last trimester of pregnancy, with no evidence of renal, cardiovascular or endocrine disease, were studied. Each patient received 9 Gm. of sodium chloride in addition to the regular hospital diet. Four of the patients demonstrated no change in blood pressure or pulse rate nor in the normal fall in blood pressure following tetraethylammonium chloride (TEAC) administration. Likewise, the administration of desoxycorticosterone acetate caused no change in cardiac output, heart size, electrocardiogram, water balance, or renal function, nor was there any indication of sodium retention or potassium loss. The excretion of 17-ketosteroids was unchanged during the period of desoxycorticosterone acetate administration, but one patient showed a significant suppression of corticosteroid excretion. Subsequent delivery in these patients was uneventful, and there was no evidence of decidual atherosis or placental infarcts comparable to those seen in toxemia. Desoxycorticosterone acetate administration in the dosage used failed to induce any of the changes seen in toxemia of pregnancy.

The fifth patient initially failed to show the usual fall in blood pressure when tetraethylammonium chloride was given, but otherwise demonstrated no abnormalities. During the three day administration of desoxycorticosterone acetate, there was a pressor response to tetraethylammonium chloride and in addition evidence of renal damage appeared. She subsequently died about six weeks later in severe renal failure, which clinically was believed to be an acute exacerbation of chronic glomerulonephritis, unrelated to the desoxycorticosterone acetate administration.

CORTELL

Hawthorne, E. W., Perry, S. L. C., and Pogue, W. G.: Development of Experimental Renal Hypertension in the Dog Following Reduction of Renal Artery Pulse Pressure without Reducing Mean Pressure. Am. J. Physiol. **174:** 393 (Sept.), 1953.

Constrictions were produced in the abdominal aorta above the renal arteries. An amount of constriction was used which produced a reduction in femoral pulse pressure, but not in the integrated mean pressure. After two to four days there was a significant rise in mean femoral blood pressure in six of seven dogs. The hypertension persisted. The authors suggest that reduction in renal artery pulse pressure may be a stimulus for the development of experimental renal hypertension.

OPPENHEIMER

Doyle, A. E., and Smirk, F. H.: The Use of the Pure Veratrum Alkaloids Neogermitrine and Protoveratrine in Hypertension. Brit. Heart J. **15**: 439 (Oct.), 1953.

The authors examined the effects of oral veratrum therapy in hypertensive individuals using Neogermitrine, Protoveratrine and various alkaloidal mixtures, and also compared the effects of protoveratrine and neogermitrine given by mouth and given by injection.

The effective dose of Neogermitrine varied from 0.4 to 1.4 mg., of protoveratrine from 0.5 to 2 mg. and of the mixed alkaloids about 5 to 10 times greater. The maximum effect of the pure alkaloid takes place within one and one-half hours as compared with two to three hours of the mixed alkaloids. The therapeutic and toxic effects of all are similar. In most instances, the difference between the therapeutic and toxic doses of the pure alkaloids was 0.1 mg.

The intravenous dose of Neogermitrine varied from 0.09 to 0.42 mg. and that of Protoveratrine from 0.19 to 0.30 mg. The maximum effect was obtained within 8 to 30 minutes. Fractional doses starting with 0.04 mg. followed by 0.12 mg. every two minutes were used. No patient responded to a subcutaneous dose who had failed to respond to oral medication.

None with basal diastolic pressures above 120 mm. Hg could be controlled for any length of time. Toxic effects appeared more frequently with continued use as the toxic and therapeutic doses approach one another.

SOLOFF

Kaplan, S. A., and Assali, N. S.: Effects of Apresoline, Veratrum Alkaloids, High Spinal Anesthesia and Arfonad on Renal Hemodynamics of Pregnant Patients with Toxemia and Essential Hypertension. Surg., Gynec. & Obst. **97**: 501 (Oct.), 1953.

Evidence has accumulated that generalized arteriolar vasoconstriction and increase in peripheral resistance to blood flow are characteristic of the hypertensive states complicating pregnancy. More recently, it has been shown that increase in vascular resistance is not limited to peripheral channels but extends also to the cerebral and renal circulations. The latter, in particular, has been subjected to careful study, and it appears that reduction of renal blood flow and glomerular filtration rate are usually present in toxemia and essential hypertension. These changes in renal hemodynamics are associated with increase in resistance of the renal vascular bed, particularly the afferent segment, to the flow of blood. The authors felt that it was of interest, therefore, to investigate the effects of some of the newer vasodepressor agents on the renal hemodynamics of subjects with these syndromes. This information should be of vast importance since it has been shown that lowering of the blood pressure of normotensive pregnant patients, for example, by autonomic blockade with high spinal anesthesia, may be accompanied by active renal vasoconstriction, and it is assumed on theoretic ground that further increase in renal vascular tone would be an undesirable side effect of a vasodepressor agent used in the management of hypertensive states complicating pregnancy.

The effects of Apresoline, veratrum preparations including Protoveratrine, Verenteral and IN-66 (from veratrum viride), high spinal anesthesia and Arfonad were investigated. Renal plasma flow, glomerular filtration rate and renal vascular resistance were determined before and after the administration of these preparations. Apresoline was administered as a single intravenous injection of 40 mg. The dose of Verenteral was 0.5 cc., of Protoveratrine 0.05 mg. in 0.5 cc. solution, and of IN-66, 1 mg. in 0.5 cc. solution. Veratrum alkaloids were administered intravenously. Arfonad was given by continuous intravenous infusion at rates varying from 6 to 16 mg. per minute. High spinal anesthesias to levels between the fourth cervical and second thoracic segments was induced in three patients with essential hypertension and three with toxemia.

As the result of this study, the authors found that Apresoline uniformly lowered the renal vascular resistance and blood pressure in cases of toxemia and essential hypertension. Neither Arfonad nor high spinal anesthesia was effective in the lowering of renal vascular resistance. In the case of the veratrum compounds, the present data indicated that there is a tendency for renal vascular resistance to increase following the administration of a crude extract or of two pure alkaloids to pregnant patients with hypertension, but, since observations were not extended beyond one hour after drug administration, information is not available on whether relaxation of renal vascular tone ultimately occurs. Previous studies have indicated that the initial renal vasoconstriction occurring with the veratrum alkaloids disappeared after about one hour, renal blood flow tending to return to normal or supernormal levels, even while hypotension persisted.

DENNISON

Ehrlich, A., Brodoff, B. N., Rubin, I. L., and Berkman, J. I.: Malignant Hypertension in a Patient with Renal Artery Occlusions. Arch. Int. Med. **92**: 591 (Oct.), 1953.

A case of malignant hypertension of short duration in a young woman with a documented history of normotension is reported with autopsy findings. A thrombotic aortic plaque with extensions into the main renal arteries, antedating the onset of hypertension, was superimposed upon a mesaortitis of unknown cause. The sudden complete occlusion of a renal artery was related in time to the onset of

malignant hypertension. The duration of the malignant hypertension was correlated with the age of the renal arterial occlusion. Arteriolonecrosis of the nonischemic kidney, brain, adrenal glands, and aorta was found. The vessels of the kidney with a completely occluded renal artery were not remarkable.

BERNSTEIN

Meilman, E.: Clinical Studies on Veratrum Alkaloids. J.A.M.A. **153:** 540 (Oct. 10), 1953.

This article describes the usefulness of Protoveratrine in the control and treatment of eclamptic toxemia as well as essential hypertension during pregnancy. Ten cases of severe preeclampsia, six of eclampsia, and one of severe essential hypertension are described. The author prefers the subcutaneous route in using Protoveratrine. The dose is determined by weight. The effective dose may be repeated at 8 to 12 hour intervals as needed. Excessive bradycardia is overcome by atropine and excessive hypotension can be overcome by a variety of pressor amines. Prompt control of headaches, scotomas, epigastric pain, convulsions and blood pressure elevation was obtained in these patients.

KITCHELL

Royce, S. W.: Hypertensive Phase of Acute Nephritis. Specific Therapy with a Derivative of Veratrum Viride. Pediatrics **12:** 358 (Oct.), 1953.

A veratrum derivative (Veriloid) was given intravenously to six children in the hypertensive phase of acute nephritis. The drug was administered in two phases: an initial, rapid infusion followed by a slow intravenous drip continued for from 9 to 22 hours. In all instances there was prompt remission of hypertension and associated complications (encephalopathy, convulsions, cardiac enlargement, anasarca and pulmonary edema). The renal and cardiac status was not affected unfavorably by treatment. The patients all appeared well and normotensive after a minimal follow-up period of 2 years. Detailed case histories are presented.

MAXWELL

Raaschou, F., and Trautner, K.: Obstruction of the Common Bile Duct in Experimental Renal Hypertension in Dogs. Scandinav. J. Clin. & Lab. Invest. **5:** 223 (No. 3), 1953.

Six dogs, made hypertensive by the Goldblatt method, showed a gradual drop in the blood pressure toward the normal, or down to a normal level, after obstruction of the common bile duct was established. The dogs were in good general condition and sufficiently fed when these falls were observed. In one hypertensive dog a sham operation upon the common bile duct did not affect the blood pressure, whereas a subsequent procedure at which the common bile duct was obstructed was followed by a gradual fall of the pressure to normal levels. Obstruction of the common bile duct did not affect the blood pressure in one normotensive dog. The cause of the fall in blood pressure in these dogs is unknown. It is suggested that the biliary obstruction may reduce the formation in the liver of a substance which is necessary for the occurrence of hypertension, such as hypertensinogen, or that the hepatic injury may result in an increased production of a substance such as the vasodepressor material of Shorr (VDM), which reduces the contraction of the arterioles.

ROSENBAUM

Bechgaard, P., and Paulsen, L.: Dihydrogenated Ergot Alkaloids (Hydergine) in the Treatment of Essential Hypertension. Acta med. scandinav. **145:** 189 (Fasc. III), 1953.

The effect of a single intramuscular dose of 0.3 mg. of Hydergine was observed in 34 hypertensive patients. A fall of 25/10 or more in the blood pressure occurred in 14 patients, with only a slight effect in 12 others, and no response in eight patients. Hydergine was less effective than hexamethonium in the same patients, particularly so far as the diastolic pressure was concerned. The fall in pressure occurred after a lapse of 10 to 15 minutes and lasted for one to two hours. Oral therapy with Hydergine was observed in 18 patients who showed some response to the parenteral medication. A slight reduction in the blood pressure was seen in only three cases and in none was there significant improvement in the electrocardiographic or retinal changes. The response to sublingual tablets of Hydergine in six patients was no more impressive than that to oral therapy.

ROSENBAUM

Grimson, K. S., Orgain, E. S., Anderson, B., and D'Angelo, G. J.: Total Thoracic and Partial to Total Lumbar Sympathectomy, Splanchnicectomy and Celiac Ganglionectomy for Hypertension. Ann. Surg. **138:** 532 (Oct.), 1953.

The results of treating 172 hypertensive patients during the past 13 years with total thoracic and partial to total lumbar sympathectomy, splanchnicectomy and celiac ganglionectomy are reviewed. The operative technic and the postoperative management are discussed. Nineteen patients were operated upon between June, 1940, and June, 1943. There were three operative deaths. Seven patients died during the tenth to thirteenth year follow-up period and nine are living. Of these nine there is a significant blood pressure reduction in six. Each of these nine patients is working with little or no disability. Ninety-five patients were operated upon between June 1943, and June 1948. In this group there was one operative death. Fifteen patients have died during this 5 to 10 year follow-up period and 79 are living. The five year survival rate of this

group was 85 per cent. Significant blood pressure reduction has persisted in 52 patients or (65.8) per cent. In the remaining 27 patients (34.2 per cent), there has been no reduction in blood pressure. Fifty-eight patients have been operated upon since June 1948. In this group there were two operative deaths, and four have died during the follow-up period (one to five years). Significant blood pressure reduction persists in 39 (75 per cent) and was not found in 21 (40.4 per cent). Of the total group of 172 operated patients 140 are now living (81.4 per cent).

An examination was made of the preoperative condition of the patients who died within three years after operation. The operation in these patients is considered to have been a failure. The conventional operative contraindications have usually been considered to be uremic encephalopathy with markedly increased intracranial pressure, serious myocardial infarction, congestive heart failure, age over 50, and marked neurosis. The preoperative condition of this group of patients varied considerably but showed advanced arterial organic vascular disease. This condition cannot be considered as a definite contraindication to operation, since some of the surviving patients exhibited similar findings. Such findings, however, do indicate a poor prognosis.

The survival rate in this series (84.5 per cent at five years, 84.2 per cent at 5 to 10 years, and 56.2 per cent at ten to thirteen years) is better than the reported follow-up studies of hypertensive patients who were not treated surgically and patients who were treated with splanchnicectomy.

SAGALL

PATHOLOGIC PHYSIOLOGY

Cotten, M. DeV.: Circulatory Changes Affecting Measurement of Heart Force in Situ with Strain Gauge Arches. Am. J. Physiol. **174:** 365 (Sept.), 1953.

There is a direct proportion between the force exerted on a strain gauge arch and the amplitude of oscillographic records obtained. Using such instruments any given area of the ventricular myocardium was shown to be a sample of changes in the whole myocardium. Tachycardia was accompanied by only very small changes in contractile force. *L*-arterenol produced definite increments in force. When augmentor nerves were stimulated both rate and force were increased in parallel fashion. Increase in initial length by 30 per cent also increased force. Beyond this amount there was no increment in force from further increase in length. Fast saline infusions had little effect.

OPPENHEIMER

Heinemann, H. O., Smythe, C. M., and Marks, P. A.: Effect of Hemorrhage on Estimated Hepatic Blood Flow and Renal Blood Flow in Dogs. Am. J. Physiol. **174:** 352, (Sept.), 1953.

Estimated hepatic blood flow was decreased to from 40 to 81 per cent of control values immediately after hemorrhage. Renal blood flow was reduced at the same time. Both parameters returned toward normal within 23 to 70 minutes. Bromosulphalein extraction and arteriohepatic vein oxygen difference increased in the period following hemorrhage.

OPPENHEIMER

Bjork, V. O., Crafoord, C., and Malmstrom, G.: Left Auricular Pressure Curve before and during First Degree Atrioventricular Block. Am. Heart J. **46:** 348 (Sept.), 1953.

The left auricular pressure curve was recorded by means of a needle inserted into the left auricle in a case of mitral stenosis with regular sinus rhythm. Cardioangiography was performed and about 60 ml. of contrast medium was injected into the left auricle in less than two seconds, resulting in a first degree atrioventricular block, that is, the atrioventricular conduction time increased from 0.16 second before the injection to a maximum of 0.29 second immediately after the injection. This block lasted for a few minutes. This event made it possible to study the auricular contraction pressure peak without interference with the pressure waves caused by the closure of the atrioventricular valve and the systolic downward movement of the atrioventricular plane. The contrasting curves are illustrated.

RINZLER

Wilson, R. H., McKenna, W. T., Johnson, F. E., Jensen, N. K., Mazzitello, W. F., and Dempsey, M. E.: The Significance of the Pulmonary Arterial Wedge Pressure. J. Lab. & Clin. Med. **32:** 408 (Sept.), 1953.

A pressure recorded through a catheter wedged tightly in a small pulmonary artery has been referred to as a "capillary," "venous," or "wedge" pressure. It was the purpose of this study to determine the significance of pressures obtained through a catheter wedged in a small pulmonary artery.

The pulmonary arterial wedge pressure was approximately equal to the left atrial pressure and it is not a measurement of the pressure in the capillaries in which the flow of blood has not been interrupted. The pulmonary venous wedge pressure was approximately equal to the pulmonary arterial trunk pressure and likewise was not a measurement of the pulmonary capillary pressure.

The difference in pressure between the pulmonary arterial trunk and pulmonary arterial wedge pressures was approximately equal to the pressure gradient across the entire lesser circulation and was employed in the calculation of the total pulmonary vascular resistance. The contour of the arterial wedge tracing did not reflect the contour of the left atrial tracing.

Particular attention should be taken in right heart catheterization to obtain an arterial wedge pressure which is accurate if pulmonary resistance or valve areas are to be calculated.

MINTZ

Soloff, L. B., and Zatuchni, J.: The Hyperactive Carotid Sinus Reflex of the Cardio-inhibitory Type in Individuals with Auricular Fibrillation. Am. J. M. Sc. **226:** 281 (Sept.), 1953.

A group of 20 consecutive patients with auricular fibrillation were examined for evidence of the hyperactive carotid sinus reflex with electrocardiographic records obtained during the period of carotid stimulation. In seven patients evidence of a cardio-inhibitory type of reflex was obtained. Three of these, each with a history of syncope, manifested ventricular standstill. In the other four, there was an abrupt slowing of the ventricular response which became regular. The ventricular complexes showed interesting changes with the transient abolition of a complete left bundle-branch block of nine years duration in one case, and an increasing amplitude of the QRS in two cases. The auricular complexes appeared unchanged. It was presumed that the predominant effect of carotid sinus pressure in these individuals was on the atrioventricular node. The hypersensitive carotid sinus is at least as common in patients with auricular fibrillation as in those with sinus rhythm.

SHUMAN

Linenthal, A. J., Winer, B. M., and Klayman, M. I.: Sinoauricular Nodal Depression and Atrioventricular Nodal Rhythm Due to Quinidine. Am. Heart J. **46:** 443 (Sept.), 1953.

A 50 year old man with premature ventricular beats and short paroxysms of ventricular tachycardia following an acute myocardial infarction was treated with quinidine sulfate which on three occasions resulted in cessation of sinoauricular control of the heart beat and the development of atrioventricular nodal rhythm. On the first two occasions, the patient was also receiving Benadryl and procaine amide hydrochloride when the nodal rhythm occurred. The third occurrence of the nodal rhythm was on the thirty-sixth hospital day. This was 10 days after the last dose of Benadryl, four days after the last dose of procaine amide and four hours and ten minutes after the last dose of quinidine. The plasma quinidine content at this time was 3.9 mg. per liter. The quinidine dosage on the day previous had been 0.6 Gm. every four hours.

Return to sinoauricular rhythm occurred within 55 minutes, 4 hours and 15 minutes, and 40 minutes on the three occasions.

RINZLER

Candel, S., and Ehrlich, D. E.: Venous Blood Flow During the Valsalva Experiment Including Some Clinical Applications. Am. J. Med. **15:** 307 (Sept.), 1953.

The authors studied the venous pathways of the arm, neck and chest of 52 young men with normal cardiovascular systems. By obtaining venograms before and during a Valsalva maneuver. During the Valsalva maneuver the radiopaque substance was frequently arrested at the level of the first rib; venograms were obtained which fulfilled the criteria for the diagnosis of venous occlusion of the axillary or subclavian vein; and a retrograde flow of radiopaque substance occurred around the shoulder joint and into the veins of the neck. In the course of diagnostic venography unintentional Valsalva maneuvers should be avoided since a venogram under these conditions might exhibit the features of venous occlusion in the presence of a normal venous system. The importance of arrest of blood flow and increased venous pressure at the level of the first rib during the Valsalva maneuver is discussed as one of the factors which might contribute to the occurrence of axillary or subclavian vein thrombosis during effort.

HARRIS

Taylor, H. B.: Transient Cardiac Arrhythmia Induced by Nonpenetrating Trauma to the Chest. Am. Heart J. **46:** 557 (Oct.), 1953.

The author presents three cases of transient cardiac arrhythmia induced by nonpenetrating trauma to the chest. In two men, aged 29 and 32 years, there was no antecedent cardiac history and the arrhythmias consisted of an auricular fibrillation with occasional ventricular extrasystoles and a supraventricular tachycardia, respectively. The third patient, a 62 year old man with asymptomatic arteriosclerotic heart disease, had frequent auricular extrasystoles. The author believes that the transient arrhythmias may be due to contusion of the right auricle in the region of the conduction system, occasioned by compression of the heart against the liver at the right pericardiophrenic angle.

RINZLER

Malmström, G., and Michas, P. A.: Oxygen and Carbon Dioxide Partial Pressures in Blood from the Systemic Circulation and the Pulmonary Capillaries. Acta med. scandinav. **145:** 91 (Fasc. 2), 1953.

In this study the oxygen and carbon dioxide partial pressures were determined in blood from the systemic circulation and from the pulmonary capillaries obtained by catheterization in 16 patients with various diseases of the heart and lungs. The pO_2 was higher in the pulmonary capillary blood than in the arterial blood, the mean difference amounting to 27.0 ± 3.0 mm. Hg. This difference between pO_2 in pulmonary capillary blood and in arterial blood was greater in that group of cases with low arterial pO_2 with a correlation coefficient

of −0.86 and a corresponding regression coefficient of −0.72. The pCO_2 was lower in pulmonary capillary blood than in the arterial blood but there was no correlation with the level of the arterial pO_2. It is suggested that study of the pO_2 and pCO_2 differences between pulmonary capillary and systemic arterial blood may be useful as a basis for a method of estimating the diffusion constant between the alveoli and the pulmonary capillaries.

ROSENBAUM

Fell, E. H., Peterson, L. F., and Chun, N.: Cardiac Arrest. Arch. Surg. **67:** 312 (Sept.), 1953.

The purpose of this paper is to encourage each surgical and anesthetic department, regardless of size or location, to develop together their skills in the dog laboratories for the prevention, recognition and treatment of the emergency of cardiac arrest. Various methods of producing obstruction to the free exchange of oxygen can then be tried, showing how easily and rapidly cyanosis and cardiac irregularities develop. When the tracheal catheter is completely occluded, the heart rate speeds up, cyanosis develops, and the heart dilates and slows. If, at this time, the airway is opened and oxygen is delivered to the lungs, a rather dramatic change is seen. The heart receives oxygen, and at once renews its work with great vigor; cyanosis clears and the heart size returns to normal.

The importance of this open airway and of oxygen to the cyanotic, dilated heart which is at the point of arrest can be beautifully shown in the dog laboratory to all members of the team involved in treating cardiac arrest.

DENNISON

Knapp, D. W., Hutt, B. K., and Horvath, S. M.: Hemodynamic Effects of Continuous Intravenous Infusion of Neo-Synephrine. Am. J. Physiol. **174:** 413 (Sept.), 1953.

In the beginning, during intravenous injection of Neo-Synephrine, there is an increase in cardiac, pulmonary and systemic pressures which is not maintained as the infusion continues. Cardiac effects were irregular and did not follow a set pattern. When pressure was high, respiration was depressed. Hematocrits, oxygen capacity and A-V differences in oxygen content were increased. There was a decrease in carbon dioxide content.

OPPENHEIMER

Birchard, W. H., and Strauss, M. B.: Factors Influencing the Diuretic Response of Seated Subjects to the Ingestion of Isotonic Saline Solution. J. Clin. Invest. **32:** 807 (Sept.), 1953.

It has previously been shown that water diuresis may follow the ingestion of isotonic saline solution by normally hydrated recumbent subjects. Since the position of the patient affects diuresis, a study was performed in healthy adult males. Under the conditions of this experiment, the ingestion of one or two liters of 0.9 per cent saline solution by seated subjects was not followed by water diuresis if the patients were normally hydrated. If the subjects had ingested excess salt on the preceding day, ingestion of a liter of saline solution was followed by prompt water diuresis. This did not occur regularly if the patients were moderately hydropenic. In one instance, when diuresis was observed, it was associated with a decreased electrolyte concentration in the urine and a decreased creatinine U/P (urine/plasma) ratio. When this type of diuretic response follows the administration of water or hypotonic solutions, it is presumed to be due to a diminished secretion of antidiuretic hormone. Since no other mechanism is known which precisely causes this type of diuresis, the hypothesis that the water diuresis is mediated through the supraopticohypophyseal system is reasonable.

WAIFE

Leaf, A., Bartter, F. C., Santos, R. F., and Wrong, O.: Evidence in Man that Urinary Electrolyte Loss Induced by Pitressin is a Function of Water Retention. J. Clin. Invest. **32:** 868 (Sept.), 1953.

Detailed metabolic studies of the effect of pitressin tannate in oil were carried out in normal man. This long-acting posterior pituitary extract produced in normally hydrated subjects prompt water retention, dilution of serum, and a marked increase in the excretion of urinary sodium and chloride. Cessation of pitressin administration was followed by a large diuresis with loss of body weight, a return of the serum concentrations to control levels, and a decrease in the urinary sodium and chloride excretion to below control levels. Since these changes were prevented by restricting fluid during pitressin administration, it would appear that the increased excretion of sodium and chloride is the result of water retention and not a direct effect of the hormone itself. The renal loss of sodium and chloride is interpreted as a homeostatic response to overexpansion of fluid volume induced by pitressin.

WAIFE

Davies, L. G., Goodwin, J. F., Steiner, R. E., and Van Leuven, B. D.: The Clinical and Radiological Assessment of the Pulmonary Arterial Pressure in Mitral Stenosis. Brit. Heart J. **15:** 393 (Oct.), 1953.

The authors studied 51 individuals with mitral stenosis, 35 of whom had aortic valvular disease and 10 mitral incompetence to determine if significant pulmonary arterial changes seen by angiocardiography could be detected on plain films and where these changes were proportional to the pulmonary arterial pressure.

Most of the changes seen on angiocardiography were seen on the conventional films. These changes were divided into three groups that corresponded to

(1) pulmonary pressure less than 40 mm. mercury which produced no changes in the film, (2) pressures between 40 to 70 mm. mercury which produced narrowing and irregularity of the basal vessels and (3) pressure greater than 70 mm. mercury which produced wide spread changes in the pulmonary blood vessels.

These arterial changes are regarded as one of the indications for valvotomy.

SOLOFF

Camara, A. A., Schoch, H. K., Reimer, A., and Newburgh, L. H.: Some Studies of the Mechanism of Intractable Edema. Arch. Int. Med. **92:** 554 (Oct.), 1953.

Data on two normal subjects emphasize again the ability of the organism to conserve sodium by tubular reabsorption of nearly all of it contained in the glomerular filtrate when only minimal amounts of sodium are ingested.

After this condition had been instituted in one of the normal subjects by sharp restriction of dietary sodium, chloride was administered, whose urinary excretion requires a nearly equivalent appearance of total base in the urine; less than one-fifth of the base requirement was supplied as sodium. During a second period of ammonium chloride administration, while the sodium intake was still restricted, the urinary sodium was even less. In another healthy subject, following a regimen that caused a marked and rapid depletion of body sodium, the contribution of sodium accompanying the increased urinary excretion of chloride, administered as ammonium chloride, fell to only 2 per cent.

The edematous nephritic patient reacted to the administered chloride by excreting only 20 per cent of it. This might be explained by the inability of the kidneys to increase production of ammonia and by the small contribution of sodium due to its very efficient reabsorption by the tubules. When tubular reabsorption of sodium was depressed by administration of a mercurial diuretic, the plentiful appearance of sodium in the urine without increase in ammonia was accompanied by a large excretion of chloride.

Studies conducted on an edematous patient with heart disease and on two normal subjects showed that under conditions of water restriction, when body water is forcibly lost through evaporation, the anticipated proportionate loss of sodium through the urine did not occur. On the contrary, calculations show that a large transfer of water from the cells into the extracellular space took place in the normal persons. In the edematous patient with heart disease no such transfer was demonstrated.

These studies indicate that both the patients with nephritis and those with cardiac disease possessed a very efficient mechanism for the renal tubular reabsorption of sodium. Since in both of the patients the volume of the extracellular fluid was excessive, one is led to conclude that the stimulus which resulted in reabsorption of sodium and water had become greatly increased. The mechanism itself in such patients may be normal and the change be merely quantitative.

DENNISON

Sjöstrand, T.: The Significance of the Pulmonary Blood Volume in the Regulation of the Blood Circulation under Normal and Pathological Conditions. Acta med. scandinav. **145:** 155 (Fasc. 3), 1953.

The author has made extensive observations of blood volume changes in the thorax and abdomen by means of plethysmographic technics and determinations of the air volume in the lungs by means of a Knipping apparatus. These studies of variations in blood distribution were done in humans. It was found that a loss of 25 per cent of the cardiopulmonary blood volume produces no measurable limitation of the respiration nor any impairment of the circulation. Furthermore, it appears that the main blood depot which can be mobilized to offset postural displacements of the blood is held in the lungs and heart. The depot blood in the lungs is considered to be taken up in the peripheral part of the venous system, that is, the veins connecting the capillaries with the larger veins. The volume of the pulmonary reservoir is three times that of the heart. This observer reports that in the intact man, contrary to reports in the experimental animal, the heart rate decreases with the increase in the amount of blood in the lungs and heart, after an initial stage of adaptation, and the heart volume at the end of systole is greater the larger its diastolic volume, indicating that the residual blood volume increases. These observations are felt to indicate that under normal circulatory conditions the heart in man, so far as frequency and stroke volume are concerned, is regulated via the vegetative nervous system. Reserve blood within the lungs is apparently held to be drawn upon to meet rapid circulatory readjustments such as are needed for producing those larger cardiac outputs which occur during physical work. The author expresses the opinion that pulmonary hypertension is not the passive result of insufficiency, but is due to an alteration in the vascular tone caused by a decrease in the stroke volume of the heart.

ROSENBAUM

PATHOLOGY

Israel, H. L.: The Pulmonary Manifestations of Disseminated Lupus Erythematosus. Am. J. M. Sc. **226:** 387 (Oct.), 1953.

A total of 22 patients in whom the diagnosis of lupus erythematosus was established by necropsy, by demonstration of the L.E. phenomenon, or by characteristic clinical and laboratory findings was studied for the presence of pulmonary or pleural

disease. In viewing the records of these patients the author has discovered a high incidence of pulmonary involvement in disseminated lupus. Pneumonia was detected in 17 instances, pleural effusions in two, and diffuse pulmonary infiltration in one; two patients had negative findings. Specific lesions such as perivascular changes, interstitial pneumonia or massive effusions were infrequent. The most common manifestation was that of pneumonia of a recurrent or migratory character, either lobar or patchy in distribution. The author concludes that disseminated lupus may present predominantly pulmonary manifestations and that patients with recurrent pneumonia, infiltrations or pleurisy should be studied for this disorder.

SHUMAN

Jurow, S. S., and Dolgopol, V. B.: Interstitial Pneumonia and Focal Myocarditis in Poliomyelitis. Am. J. M. Sc. **226**: 393 (Oct.), 1953.

Interstitial pneumonia was found to be present in 31 cases of 121 poliomyelitis victims examined at necropsy. In 13 there was evidence of other forms of pneumonia elsewhere within the lungs. Interstitial pneumonia was characterized by a peribronchial and bronchial mucosal infiltration of lymphocytes extending out to the adjacent alveolar walls. Hyaline membranes were not observed in the alveoli. Myocarditis was demonstrated in 24 cases (32.8 per cent) of 73 patients from whom multiple sections of myocardium were available. The inflammatory foci, located in the interventricular septum, papillary muscles, auricular walls and elsewhere, consisted of infiltrations of histocytes, polymorphonuclear leucocytes, lymphocytes with edema and hemorrhages. The possibility of viral etiology of myocarditis, as well as pneumonitis, remains a possibility for which further work is necessary to establish as fact. The pulmonary changes could be produced by aspiration of regurgitated gastric contents.

SHUMAN

OTHER SUBJECTS

Kuhns, W. J., and Bauerlein, T. C.: Exchange Transfusion in Hemolytic Anemia Complicating Disseminated Lupus Erythematosus. Arch. Int. Med. **92**: 284 (Aug.), 1953.

The case of a patient with acquired hemolytic anemia and acute disseminated lupus erythematosus is reported. During the course of multiple whole blood transfusion therapy the patient developed three demonstrable atypical serum antibodies—anti-C, anti-A, and another incompletely identified hemagglutinin. These apparently were the agents responsible for her hemolytic disease. Because of increasing intravascular hemolysis, anemia, and renal insufficiency, the patient was given an exchange transfusion, with immediate beneficial results. The ultimate picture was complicated by persistence of the underlying disease and the bizarre serological pattern, which largely precluded blood group compatibility in the course of subsequent transfusions. Certain aspects of serological behavior in relation to this case are discussed.

BERNSTEIN

Wylie, B.: Toxemia of Pregnancy and Altered Renal Circulation. Am. J. Obst. & Gynec. **66**: 254 (Aug.) 1953.

A theory is presented in this paper to account for the toxemia of pregnancy. Pregnancy, it is claimed, produces a mechanical interference with the renal circulation. If this interference is mild, only hypertension, proteinuria and edema will develop; if severe, coma, convulsions, anuria, uremia and hemorrhage will supervene. Therapy aimed at removing the interference with the renal circulation is recommended.

WESSLER

Whiting, W. B., and Millar, M. S.: Cation Exchange Resins. Texas J. Med. **48**: 585 (Aug.), 1952.

Based on clinical observation of between 200 and 300 cases of congestive failure of varying degree, the authors believe that sulfonic acid resins are better tolerated by the patients than are the carboxylic acid resins. The ammonium form is not usually objectionable. Fecal impactions are easily avoided but occasionally occur. With doses ranging from two to five ounces of resins daily over prolonged periods no untoward symptoms have been encountered. There have been no cases of potassium deficiency nor of vitamin deficiency. One case of clinically apparent acidosis was encountered in a patient with advanced nephritis. Only three patients stubbornly refused to take the resin. In a few it was discontinued as a matter of choice. The majority of patients were maintained on a low sodium regimen and most received periodic injections of mercurial diuretics. The low salt syndrome did not occur in any of these cases.

Success with the clinical use of cation exchange resins depends to a great extent on the astuteness of the physician, his familiarity with the principles of fluid and electrolyte balance, and his awareness of the pathologic physiology underlying the disease which he is treating.

BERNSTEIN

Croxatto, H., Vera, C., and Barnafi, L.: Inactivation of Antidiuretic Hormone by Blood Serum of the Pregnant Woman. Proc. Soc. Exper. Biol. & Med. **83**: 784 (Aug.–Sept.), 1953.

The results obtained with the blood sera of 50 pregnant women indicate that in the course of pregnancy there is a progressive increase in the enzymatic activity responsible for the destruction of the antidiuretic properties of vasopressin. In the last week of pregnancy 0.1 ml. of blood serum destroys

300 to 350 mU of vasopressin in the course of 40 to 50 minutes, whereas the same amount of blood serum of a nonpregnant woman inactivates only 30 to 35 mU in 960 minutes.

The "antidiuretasic activity" (activity responsible for the destruction of the antidiuretic properties of vasopressin) rapidly decreases in the postpartum period and reaches the values preceding pregnancy five or six days after delivery.

MINTZ

Slattery, R. V.: Heart Disease Discovered on Chest Microfilms. J. A. M. A. **152:** 1595 (Aug. 22), 1953.

In surveys of large numbers of persons for pulmonary tuberculosis it has been noted that many cardiac as well as pulmonary abnormalities were found, and, as a result, it has been recommended that the microfilms be used for surveys for the detection of heart disease. The paper discusses the incidence of heart disease in 682 persons having chest microfilms. On subsequent clinical investigation 56 of these patients had evidence of heart disease, but only 25 of the 56 with heart disease were noted as having abnormal hearts on the microfilms. Twelve persons who were thought to have abnormal cardiac silhouettes did not prove to have heart disease on clinical study. Because of this low degree of detection, the microfilm is therefore not recommended for use in large surveys for finding persons with heart disease.

KITCHELL

Nabarro, J. D. N.: Cardiac Involvement in Malignant Lymphoma. Arch. Int. Med. **92:** 258 (Aug.), 1953.

Pathologic evidence of cardiac involvement in cases of malignant lymphoma is not uncommon. Clinical reports describing this involvement are few. When cardiac abnormalities are the presenting feature of a lymphoma the diagnosis is difficult, but when they occur in patients known to be suffering from the disease, the possibility of their neoplastic origin always should be considered. The two commonest clinical pictures are that of intractable congestive cardiac failure and that resulting from a pericardial effusion. Treatment by irradiation has proved disappointing.

Three cases are described. In one, wherein the patient presented intractable congestive failure due to reticulosarcoma, the diagnosis was made by biopsy of a skin nodule. The tumor was highly radiosensitive, but treatment was unsuccessful. In the second case, pericarditis with effusion developed in the course of Hodgkin's disease, and in the third there was a complicated picture of hypertension and pericardial fibrosis which gave rise to congestive failure in the terminal stages of the disease.

BERNSTEIN

Lovingood, C. G., and Patton, R.: Translumbar Aortography as a Diagnostic Aid in Localizing Arterial Emboli. Arch. Surg. **67:** 164 (Aug.), 1953.

The authors present five cases of peripheral arterial embolism in which aortography accurately localized the block. They conclude that the technic provides a practical, safe and rapid means of establishing the diagnosis.

WESSLER

Sadove, M. S., Wyant, G. M., and Gittelson, L. A.: The Acute Hypoxic Episode. Brit. M. J. **2:** 255 (Aug. 1), 1953.

In discussing the acute episodes of cerebral hypoxia such as those which accompany cardiac standstill and other cardiac accidents during operation, the authors emphasize the vicious cycle of hypoxia and edema which is likely to develop in the brain and the hypoxia-potentiating effects of edema. They recommend dehydration by concentrated glucose solution, half- or quarter-reconstituted dried plasma, or concentrated human albumin. They present the case of a patient in coma following cardiac standstill and resuscitation who several times regained consciousness promptly although briefly when injections of 50 per cent glucose were given.

MCKUSICK

AMERICAN HEART ASSOCIATION, INC.

44 East 23rd Street, New York 10, N. Y.
Telephone GRamercy 7–9170

RESEARCH AWARDS ANNOUNCED

A total of 169 research awards in the amount of $953,370.71 has been approved by the Association's Board of Directors upon recommendation of the Research Committee of the Scientific Council. These provide for studies during the 1954–55 fiscal year by three Career Investigators, 19 continued Established Investigators, 20 new Established Investigators, the renewal of 16 Research Fellowships, 24 new Research Fellowships, 68 new Grants-in-Aid and 19 continued Grants-in-Aid.

These awards represent an increase of approximately $150,000 over the sum allotted by the Association to the national program of research support last year. They bring to nearly $8,000,000 the total the Association and its affiliates have provided for this purpose in the six years since it became a voluntary health agency. The number of applications received increased by nearly two-thirds.

The current allocations by the Association and its affiliates are made from public contributions to the 1953 Heart Fund campaign. The national headquarters allots at least 50 per cent of its total income to the national research support program. Affiliate heart associations, in addition to participating in the national program, also make research awards to support additional scientific investigations in their own areas.

The latest awards were made as follows:

Career Investigators

Lorber, Victor, University of Minnesota Medical School, Minneapolis.

Pappenheimer, John, Harvard Medical School, Boston.

Coons, Albert H., Harvard Medical School, Boston.

Continued Established Investigators

Nikawa, Jerry Kazuo, immunophysiology, University of Colorado School of Medicine, Denver.

Koch, Edward H., a study of the living microscopic blood flow and vessel walls in patients and experimental animals with thromboembolic phenomena. Western Reserve University, Cleveland.

Cohn, Mildred, mechanisms of phosphorylation and phosphate transfer reactions; Washington University School of Medicine, St. Louis.

Curran, George Lally, the metabolic aspects of cardiovascular disease with particular reference to lipid metabolism, University of Kansas Medical School, Kansas City.

Edelman, Isidore Samuel, body water and electrolytes studied with tracers, University of California School of Medicine, San Francisco.

Elkinton, J. Russell, cardiovascular physiology, University of Pennsylvania, Philadelphia.

Fishman, Alfred P., cardiodynamic and renal interplay in the production of congestive heart failure, Cardio-Pulmonary Laboratory, Bellevue Hospital, New York.

Gergely, John, energetics and contractile proteins of heart muscle, Massachusetts General Hospital, Boston.

Grisolia, Santiago, enzymatic patterns of nitrogen metabolism in heart muscle. University of Kansas Medical School, Kansas City.

Lepeschkin, Eugene, electro-physiological interpretation of the normal and pathological ventricular complex of the electrocardiogram. University of Vermont, Burlington.

Merrill, John P., the further development of the artificial kidney as a therapeutic and investigative tool in cardiovascular and renal disease, Peter Bent Brigham Hospital, Boston.

Metcalfe, James, changes in the maternal circulation during pregnancy and labor. Boston Lying-in Hospital.

Mommaerts, Wilfried F. H. M., biochemistry of muscular contraction, Western Reserve University School of Medicine, Cleveland.

Peterson, Lysle Henry, volume pressure, "distensibility" of intact veins, arterial circulation with view to calculating stroke volume, integration of peripheral c-v-reflexes. University of Pennsylvania, Philadelphia.

Plaut, Gerhard W. E., pathways and compounds of intermediary metabolism with particular regard to the properties of heart muscle. University of Wisconsin, Madison.

Stamler, Jeremiah, experimental atherosclerosis; experimental hypertension, renal function in edema formation. Michael Reese Hospital, Chicago.

Stefanini, Mario, establishment of "profile" of tests for diagnosis of thrombotic tendency; relation of the endocrine system to the blood coagulation mechanism and the pathogenesis of thromboembolism; possibilities of employment of fibrinolysin

in the treatment of thromboembolism; New England Center Hospital, Boston.

Stetson, Chandler A., investigations in rheumatic fever; University of Minnesota.

Tobian, Louis, Jr., 1. the relation of steroids and sodium to hypertension; 2. the role of steroid intoxication in toxemia of pregnancy; 3. the role of emulsifying forces in plasma in atherosclerosis, Southwestern Medical School of the University of Texas, Dallas.

New Established Investigators

Calvert, Henry Mead, metabolism and permeability of heart tissue investigated with isotopic techniques, University of Minnesota Medical School, Minneapolis.

Conn, Jr., Hadley L., a study of the alterations in pressure-volume-flow relationships within the cardiovascular system produced by direct cardiovascular stresses; and the effect of these alterations on transcapillary kinetics and organ metabolism; University of Pennsylvania Medical School, Philadelphia.

Drell, William, biochemical studies of the sympathetic nervous system in relation to cardiovascular function; University of California School of Medicine, Los Angeles.

Eckstein, Richard W., the coronary collateral circulation. The oxygen consumption of the right ventricle; Western Reserve University School of Medicine, Cleveland.

Gaudino, Mario, studies on the intra and extracellular distribution of water and electrolytes in the organism as a whole and in tissues by means of radioactive indicators; New York University College of Medicine.

Goodall, McChesney, 1. effect of cervicostellate ganglionectomy on the adrenaline and noradrenaline content of sheep heart. 2. unknown sympatholytic factor present in mammalian heart; Yale University Medical School, New Haven.

Goodyer, Allan V. N., hemodynamic factors affecting electrolyte metabolism and the renal excretion of electrolytes; Yale University School of Medicine, New Haven.

Kaplan, Melvin H., attempt to localize tissue-deposited streptococcal antigens and antibodies in animal and human tissues by means of the fluorescein-labelling technique—possible application to study of the pathogenesis of cardiac and skin lesions in rheumatic fever; House of the Good Samaritan and Children's Medical Center, Boston.

Mann, George V., the cause and prevention of atherosclerosis; Harvard School of Public Health, Boston.

Mateer, Frank M., 1. cardiovascular effects of specific electrolyte depletion and repletion studied by means of dialysis technique; 2. ballistocardiographic studies in the normal and abnormal subject; University of Pittsburgh School of Medicine.

Mathews, Martin B., the physical chemistry of the acid mucopolysaccharides of connective tissue and their protein complexes; University of Chicago.

Osborn, John J., extra-corporeal circulation, physiology of hypothermia, and intra-cellular fluid and ionic shifts during respiratory acidosis; New York University College of Medicine.

Rose, John C., 1. studies of the circulation in the dog using a mechanical left ventricle; 2. a sonic flowmeter; 3. studies in aortic insufficiency; 4. studies on the relationship between arterial pressure and cardiac auscultatory phenomena; Georgetown University Medical Center, Washington, D. C.

Sanadi, D. Rao, studies on (1) oxidative phosphorylation and (2) amino acid metabolism; University of Wisconsin, Madison.

Schmidt-Nielsen, Bodil M., comparative kidney physiology; Duke University School of Medicine, Durham, N. C.

Singer, Thomas P., studies on oxidative metabolism of sulfur amino acids in animals; studies on metabolism and function of new coenzymes; Institute for Enzyme Research, University of Wisconsin, Madison.

Sprinson, David B., (a) biochemistry of one-carbon intermediates. (b) biosynthesis of aromatic compounds in bacteria; Columbia University College of Physicians and Surgeons, New York.

Stavitsky, Abram B., studies on the basic mechanisms of antibody production *in vivo* and *in vitro;* Western Reserve University School of Medicine, Cleveland.

Wessler, Stanford, the pathogenesis of intravascular thrombosis; Beth Israel Hospital, Boston.

West, John R., studies on the physiologic basis of reduced work tolerance in heart disease; Cardio-Pulmonary Laboratory, Presbyterian Hospital, New York.

Renewal Research Fellows

Abelmann, Walter H., cardiovascular dynamics in hepatic disease and related disorders and their determinants; under Laurence B. Ellis, Thorndike Memorial Laboratory, Boston.

Balchum, Oscar J., pulmonary-circulatory hemodynamics in congenital and acquired heart disease, under S. Gilbert Blount, University of Colorado, Denver.

Briller, Stanley Arthur, energetics of the myocardium, under Charles E. Kossmann, New York University College of Medicine.

Camara, Augusto A., studies of changes in the volume, concentration and composition of the extracellular fluid in patients with heart disease with edema, and with oliguria or anuria with special reference to acid-base balance, under Agerico B. M. Sison, University of the Philippines, Manila.

Conrad, Loyal Lee, a study of antilipemia factors and other aspects of lipid metabolism in atherosclero-

sis; under Robert H. Furman, Oklahoma Medical Research Institute, Oklahoma City.

Cugell, David Wolf, abnormalities of respiration in diseases of the heart and lungs, under Theodore L. Badger and L. B. Ellis, Thorndike Memorial Laboratory, Boston.

Dontas, Anastasius S., electrical study of ganglionic and adrenergic blockade. Dynamics of prolonged altered homeostasis in the cardiovascular system, under M. H. Seevers, University of Michigan Medical School, Ann Arbor.

Englard, Sasha, studies on the mechanism of electron transfer from reduced diphosphopyridine nucleotides to flavoproteins; under Sidney P. Colowick, McCollum Pratt Institute, Johns Hopkins Hospital, Baltimore.

Khairallah, Philip Amin, (1) chemical investigation on conduction in the purkinje tissue, (2) a correlation between metabolism and electrocardiography under W. F. H. M. Mommaerts, Western Reserve University School of Medicine, Cleveland.

Ling, Johnson, S. L., studies on the pulmonary circulation, cardio-pulmonary reflexes, pulmonary congestion and pulmonary edema, under Carl F. Schmidt, University of Pennsylvania School of Medicine, Philadelphia.

Nelson, Clifford V., the relationship between individual cardiac fiber response and the electrocardiogram, under Hans H. Hecht, University of Utah Medical School, Salt Lake City.

Rapaport, Elliot, pulmonary and splanchnic blood volumes in normal individuals and in those with congestive heart failure, under Lewis Dexter, Peter Bent Brigham Hospital, Boston.

Rakita, Louis, the nature of the repolarization process in the normal heart following acute coronary occlusion, under Roy W. Scott, Cleveland City Hospital.

Skelton, Floyd Reginald, the role of certain androgenic steroids in the production of experimental hypertension and cardiovascular-renal disease, under Robert E. Stowell, University of Kansas, Kansas City.

Von Korff, Richard W., studies in intermediary metabolism I. The effect of alkali metal ions on acetate metabolism, under Lewis Thomas, University of Minnesota, Minneapolis.

Warner, Homer R., relationship of heart rate to cardiac output in normal subjects and in patients with heart disease, studied with the pressure pulse method, under Hans H. Hecht, University of Utah, Salt Lake City.

New Research Fellowships

Brewster, Jr., William R., the metabolic and hemodynamic effects of the general anesthetic agents, including the muscle relaxant drugs and the vasopressor amines, under Dean A. Clark, Massachusetts General Hospital, Boston.

Childs, Alfred W., the relation of glomerular filtration rate to the distribution of excretory delay in man, under Stanley E. Bradley, Columbia University College of Physicians and Surgeons, New York.

Done, Alan K., the relation of salicylates to the adrenal cortex and its secretions, under Vincent C. Kelley, University of Utah, Salt Lake City.

Eckstein, John W., postoperative physiological studies in patients with congenital cardiovascular disease, under James W. Culbertson, State University of Iowa, College of Medicine, Iowa City.

Flavin, Jr., Martin, a study of some enzymes concerned with fatty acid metabolism, under Severo Ochoa, New York University.

Friedman, Edward W., bacterial factor in traumatic shock, under Jacob Fine, Beth Israel Hospital, Boston.

Gibson, William, pathology of the heart and its relation to the clinical manifestations of congestive failure, under Herman L. Blumgart, Harvard University, Boston.

Goldstein, Franz, the role of hypermetabolism in hypertension, under Garfield G. Duncan, Pennsylvania Hospital, Philadelphia.

Gotch, Frank A., fluid and electrolyte composition in patients with essential hypertension studied with Na^{24}, K^{42}, D_2O and Thiosulfate, under Isidore S. Edelman, University of California Medical School, San Francisco.

Gunn, Jr., Chesterfield G., studies of the central nervous system's role in experimental hypertension, under H. W. Magoun, University of California Medical Center, Los Angeles.

Jardetzky, Oleg, study of turnover of high-energy phosphate of the mammalian heart under normal conditions and in failure with the aid of radioactive phosphorus (P^{32}), under Victor Lorber, University of Minnesota, Minneapolis.

Lamb, Lawrence E., spatial vectorcardiography, under Pierre W. Duchosal, University of Geneva.

Nitzberg, Saul I., relationship of stress erythrocytosis and polycythemia vera to the occurrence of thromboembolism (with particular reference to coronary thrombosis); under William Dameshek, New England Center Hospital, Boston.

Padawer, Jacques, the physiology of the mast cell and its relation to cardiovascular disease, under Albert S. Gordon, New York University.

Porter, Richard, factors governing the distribution of acid among the intra- and extra-cellular spaces, under William B. Schwartz, New England Center Hospital, Boston.

Reiss, Oscar K., isolation of a hypocholesteremic factor from brain and investigations of its mode of action, under Richard J. Jones, University of Chicago.

Rudolph, Abraham M., studies on the mechanism of sodium retention in valvular lesions of the dog's heart with and without cardiac failure, under C.

Barger and E. Landis, Harvard Medical School, Boston.

Sharp, John T., hemodynamic studies in valvular heart disease, under David G. Greene, University of Buffalo School of Medicine.

Sheppard, Erwin, electrostatic forces involved in blood coagulation, under Irving S. Wright, Cornell University Medical Center, New York.

Spurr, Gerald B., cardiovascular adjustments to prolonged, profound hypothermia, under Steven M. Horvath, State University of Iowa, Iowa City.

Surawicz, Borys, studies of genesis and mechanism of the electrocardiographic patterns of electrolyte imbalance, under Samuel Bellet, Philadelphia General Hospital.

Walker, Wilbur G., estimation of plasma volume in patients with congestive heart failure using exponential analysis of plasma disappearance curve of labelled proteins, under A. McGehee Harvey, E. Cowles Andrus and Theodore Enns, Johns Hopkins Hospital, Baltimore.

Weiss, Samuel B., synthesis of phosphatides in isolated mitochondria I: incorporation of isotopically labeled phosphatidic acids, under Eugene B. Kennedy, Ben May Laboratory for Cancer Research, Chicago.

Wennesland, Reidar, studies of blood volume in normal and pathologic states. A comparison of methods using T-1824, carbon monoxide and Cr 51, under James Hopper, Jr., University of California Medical School, San Francisco.

Continued Grant Awards

Council on Rheumatic Fever and Congenital Heart Disease, for cooperative research study of the relative effectiveness of ACTH and Cortisone in the treatment of rheumatic fever and the prevention of rheumatic heart disease. *David. D. Rutstein*, Chairman, $4,000.00

Emory University School of Medicine, Atlanta, for the study of the nature of the vascular response to sodium restriction, by *Eugene B. Ferris* and *Albert A. Brust*, $5,250.00

University of Pittsburgh School of Public Health, for the study of congestive heart failure due to valvular disease upon myocardial metabolism in dogs, by *Robert E. Olson*, $8,925.00

New England Center Hospital, Boston, for the study of the relation of the endocrine system to the blood coagulation mechanism and to the pathogenesis of thromboembolism; possibilities of employment of fibrinolysin and fibrinolytic substances in the treatment of thromboembolism, by *Mario Stefanini*, $5,250.00

Michael Reese Hospital, Chicago, for the study of factors regulating renal function and electrolyte metabolism in experimental venous congestion with edema, by *Jeremiah Stamler*, $4,200.00

La Rabida Jackson Park Sanitarium, Chicago, for the study of the nature and mode of action of the substance in testicular extract causing increased vascular permeability, by *Earl P. Benditt*, $5,376.00

Hospital of the University of Pennsylvania, Philadelphia, for the study of the urinary metabolites of C-21 cortical steroids determined by paper chromatographic methods, by *F. Curtis Dohan*, $7,875.00

Faculty of Medicine, McGill University, Montreal, for the study of chemical analyses of the aorta and tissue lipids during the earliest stages of the development of experimental atherosclerosis: Their correlation with histo-chemical observations, by *G. Lyman Duff*, $6,819.75

Indiana University School of Medicine, Bloomington, for the study of immunochemical and physical analysis of the time of appearance, distribution mechanism of synthesis and interaction of the contractile proteins, actin and myosin, in the morphogenesis of the heart, by *James D. Ebert*, $3,927.50

State University of Iowa College of Medicine, Iowa City, for the study of cardiovascular adjustments to the sudden acute occlusion of the thoracic aorta and/or one or both of the Vena Cava, by *Steven M. Horvath*, $5,250.00

University of Tennessee College of Medicine, Memphis, for the study of the role of the heart, blood vessels, liver and altered body fluids in the hypertension arising in dogs living a month or longer without kidneys, by *C. Riley Houck*, $7,980.00

University of Chicago School of Medicine, for the identification of the hypocholesteremic agent in a brain extract and studies on its mode of action, by *Richard J. Jones*, $5,250.00

Oklahoma Medical Research Institute, Oklahoma City, for the study of the influence of adrenal cortical hormones on cardiac lesions and enzymes, by *Charles D. Kochakian*, $5,433.75

Harvard Medical School, Boston, for the study of the circulatory action of the esters of protoverine and of germine, by *Otto Krayer*, $7,875.00

Harvard Medical School, Boston, to study the partial synthesis of hypertensive veratrum alkaloids, by *S. Morris Kupchan*, $4,181.10

Washington University School of Medicine, St. Louis, Missouri, for the study of experimental collagen disease. Functional and anatomic responses of the cardiovascular system in experimental animals to repeated antigenic assaults administered by various routes, by *John R. Smith*, $3,465.00

Cornell University Medical College, New York, for the study of the distribution of electrolytes in acute renal failure, by *Roy C. Swan*, $5,250.00

Duke University School of Medicine, Durham, for the study of the response of the pulmonary vascular bed to hemodynamic alterations in the systemic circulation, by *James V. Warren*, $5,250.00

New York University College of Dentistry, for the study of the relation of platelet function to blood coagulation, with particular reference to platelet morphology, release of vaso-constrictor substance

from the platelets and the formation of hemostatic platelet plugs in rats with coagulation disorders, by *Marjorie B. Zucker*, $4,620.00

New Grant Awards

University of Colorado School of Medicine, Denver, for the study of immunophysiology, by *Jerry K. Aikawa*, $3,150.00

University of Minnesota Hospital, Minneapolis, for the study of the effect of liver injury on the water exchange and electrolyte excretion in rats with diabetes insipidus, by *Carl S. Alexander*, $2,625.00

Medical College of Alabama, Birmingham, for the study of myocardial metabolism; action of digitalis on cardiac proteins, by *Richard J. Bing*, $6,300.00

Western Reserve University, Cleveland, for the study of the *in vivo* control of erythrocyte aggregation, I. the influence of surface active agents on erythrocyte aggregation and the mechanism of the reaction of particulate matter with the blood and liver analyzed *in vivo* at the microscopic level, by *Edward H. Bloch*, $3,150.00

State University of New York College of Medicine, Brooklyn, for the study of the hemodynamic effects of pyrogens upon the circulation during shock with special reference to the renal shut-down associated with shock, toxemia and incompatible blood transfusions, by *J. Leonard Brandt*, $4,200.00 (partially sponsored by the Orange County, New Jersey, Heart Association)

University of Minnesota, Minneapolis, for the study of experimental myocarditis and valvulitis, by *Joel G. Brunson*, $4,725.00

University of Minnesota, Minneapolis, for the study of metabolism of cardiac tissue investigated with isotopic techniques, intermediates of propionate, lactate, and pyruvate metabolism in cardiac tissue, by *H. Mead Cavert*, $4,200.00

Fels Research Institute, Antioch College, Yellow Springs, for further studies with the dispersion oxygenator (artificial heart-lung), by *Leland C. Clark*, $5,250.00

Temple University Medical School, Philadelphia, for the study of the continuation of research on preparation and study of angiotonase (hypertensinase), by *Dean A. Collins*, $4,200.00

University of Pennsylvania School of Medicine, Philadelphia, for the study of the utilization of radio isotope techniques in the study of the "cardiac failure shock" state incident to acute cardiovascular stress, by *Hadley L. Conn, Jr.*, $4,200.00

George Washington University, Washington, D. C., for the study of the nature of desoxycorticosterone inhibition of the heart and its reversal by serum, by *Ivor Cornman*, $3,780.00

State University of Iowa Hospital, Iowa City, for the study of the effects of surgical and drug therapy on hepatic and renal circulation and function in certain cardiovascular disorders (continuation of currently supported investigation), by *James W. Culbertson*, $5,250.00

University of Pittsburgh School of Medicine, for the study of cardiovascular effects of specific electrolyte depletion and repletion studied by means of dialysis technic, by *T. S. Danowski*, $5,250.00

Columbia University College of Physicians and Surgeons, New York, for the studies of plastic prostheses for blood vessel replacement and aortic insufficiency, study of cardiac function during hypothermia, by *Ralph A. Deterling, Jr.*, $4,200.00

University of Michigan, Ann Arbor, for the study of ganglionic and adrenergic blockade. Dynamics of prolonged altered cardiovascular homeostasis, by *Anastasius S. Dontas*, $3,150.00

University of California Medical Center, San Francisco, for the study of the distribution, penetration and rates of exchange of sodium, potassium and water in the gastrointestinal tract, measured with Na24, K42 and D20 and with particular reference to the effects of experimentally induced sodium depletion, potassium depletion, acidosis and alkalosis, by *Isidore S. Edelman*, $5,250.00

Hospital of the University of Pennsylvania, Philadelphia, for the studies on the supra-opticohypophyseal system in the normal dog and cat pertaining to volume regulation; an effort to provide at least a partial explanation of certain phenomena observed in markedly edematous patients with heart disease, by *J. Russell Elkinton*, $3,055.50

State University Medical Center at Syracuse University School of Medicine, Syracuse, for the study of action in the heart lung preparation of the dog and factors influencing the after stimulation contraction in the isolated auricle, by *Alfred E. Farah*, $4,200.00

American University of Beirut, Beirut, Lebanon, for the study of the effect of krebs cycle inhibitors and metabolites on the performance and metabolism of the isolated mammalian heart (heart-lung preparation), by *George Fawaz*, $4,725.00

Cardio-Pulmonary Laboratory, Bellevue Hospital, New York, for the study of the pulmonary blood flow during graded exercise; the circulating blood volume in patients with cardiac disease, by *Alfred P. Fishman*, $5,250.00

Harold Brunn Institute, Mount Zion Hospital, San Francisco, for studies concerning the metabolism of cholesterol, by *Meyer Friedman* and *Sanford O. Byers*, $5,250.00

Washington University School of Medicine, St. Louis, for the study of metabolic factors in experimental heart failure, by *Robert F. Furchgott*, $4,200.00

Johns Hopkins Hospital, Baltimore, for the study of modification of tachycardia and hypertension psychogenically produced by changing excitatory into inhibitory stimuli, by *W. Horsley Gantt*, $5,250.00

New York University College of Medicine, for

the studies on the intra and extracellular distribution of electrolytes in the organism as a whole and in tissues by means of radioactive indicators, by *Mario Gaudino*, $4,200.00

University of Minnesota, Minneapolis, for studies on the mechanisms involved in the development of necrotizing lesions of the skin, heart, kidneys and blood vessels, by *Robert A. Good*, $6,300.00

Yale University School of Medicine, New Haven, for the study of hemodynamic factors affecting the metabolism and renal excretion of electrolytes; the influence of electrolyte abnormalities on the circulatory response to stress, by *Allan V. N. Goodyer*, $4,200.00

Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, for the study of an analysis of the mechanism by which epinephrine produces vasodilation including a study of the reversal induced by adrenergic blocking drugs, by *Harold D. Green*, $4,725.00

University of Mississippi School of Medicine, University, Miss., for the study of the development of methods for continuous recording of cardiac output, by *Arthur C. Guyton*, $5,066.25

Tulane University School of Medicine, New Orleans, for the study of cardiovascular and metabolic adjustments of the rat concerned with the development of resistance to physical trauma in the noble-collip drum, by *John K. Hampton, Jr.*, $4,777.50

Howard University School of Medicine, Washington, D. C., for the study of the effect of chronic pulmonary disease and chest surgery upon pulmonary and cardiac function, by *K. Albert Harden*, $4,436.25

University of Utah College of Medicine, Salt Lake City, for the study of pharmacology, physiology and biochemistry of the heart; research on the mechanism of action of digitalis, by *Stewart C. Harvey*, $6,300.00

Western Reserve University School of Medicine, Cleveland, for the study of the regulation of blood lipid concentration with special reference to pathogenesis of nephrotic hyperlipemia, by *Walter Heymann*, $6,300.00

University of North Carolina School of Medicine, Chapel Hill, for the study of the effect of partial substitution of the nitrate ion for the chloride ion on circulation and electrolyte balance with special reference to hypertension and edema, by *Edwin P. Hiatt*, $5,250.00

Providence College, Providence, for the study of labile digitonin precipitable metabolites of acetate in the chick embryo and living rat liver tissue, normal, regenerating and tumorous, by *Reverend Frederick C. Hickey*, $2,103.86

Instituto de Biologia y Medicina Experimental, Buenos Aires, for studies on experimental high blood pressure, by *Bernardo A. Houssay*, $10,000

Johns Hopkins University, Baltimore, for the study of the influence of the environment on the affinity of hemoglobin for oxygen, by *Walter J. Hughes*, $6,300.00

Harvard University School of Public Health, Boston, for the laboratory and epidemiologic investigation of congenital heart disease, by *Theodore H. Ingalls*, $4,200.00

Wayne University College of Medicine, Detroit, for the study of electrolyte disturbances in cardiac and renal failure, by *Lloyd T. Iseri*, $5,000

Massachusetts General Hospital, Boston, for the study of the biological significance of the sulfate group in heparins, by *Roger W. Jeanloz*, $5,250.00

Michael Reese Hospital, Chicago, for the study of coronary circulation, cardiac energetics and myocardial metabolism, by *Louis N. Katz*, $8,190.00

University of Utah, Salt Lake City, for the study of adrenal hormones in the blood of patients with rheumatic fever and related conditions, by *Vincent C. Kelley*, $4,200.00

University of South Dakota, Vermillion, for the study of biosynthesis and purification of high specific activity radiodigitoxin, by *F. E. Kelsey*, $5,670.00

Duke Hospital, Durham, for the study of the metabolism of acid mucopoly-saccharides of ground substance, by *Grace P. Kerby*, $4,200.00

University of Minnesota, Minneapolis, for the study of the relation between mode of life, particularly diet and physical activity, to the development of degenerative heart disease, as exemplified in different populations, by *Ancel Keys*, $5,250.00

New York University College of Medicine, for the study of correlation of intracellular potential variations of the single ventricular fiber with mechanical function of the ventricles, by *Charles E. Kossmann*, $2,798.25

Yale University School of Medicine, New Haven, for the study of the measurement of renal blood volume in man, by *Willoughby Lathem*, $4,200.00 (partially sponsored by The Heart Committee, Greenwich Health Association, Greenwich, Conn.)

Massachusetts General Hospital, Boston, for the study of the volume of distribution of a large water load; the site of action of cortisone on water excretion, by *Alexander Leaf*, $5,250.00

Montefiore Hospital, New York, for the study of the use of a method of measuring lower extremity blood flow (muscle flow), to study the peripheral circulation and to measure certain aspects of muscle metabolism in normal subjects and cardiac patients, by *Louis Leiter*, $5,775.00

University of Cincinnati, for the study of the nature of the reabsorptive mechanism for inorganic sulfate in the normal kidney, by *William D. Lotspeich*, $4,095.00 (fully sponsored by the Youngstown Area Heart Association, Youngstown, Ohio)

Washington University School of Medicine, St. Louis, for the study of the isolation of specific heart

constituents which bind drugs, by *Oliver H. Lowry*, $3,150.00

Peter Bent Brigham Hospital, Boston, for an investigation of the relation of renal failure to certain disorders of the cardiovascular system, by *John P. Merrill*, $5,250.00

Johns Hopkins Hospital, Baltimore, for the study of factors governing the dye-dilution curve in the presence of cardiovascular shunts, by *William R. Milnor*, $4,200.00

University of California, Berkeley, for a detailed study of the cardiovascular anomalies of rat embryos from mothers deprived of pteroylglutamic acid (PGA) from the 9th to the 11th days of gestation, by *Ian Whitelaw Monie*, $4,200.00

New York University College of Medicine, for the study of extracorporeal blood circulation and oxygenation, alone and in conjunction with hypothermia, for direct intracardiac surgery, by *John J. Osborn*, $5,250.00

Mount Zion Hospital, San Francisco, for the study of the role of potassium in maintenance of blood pressure and peripheral vascular reactivity in normotensive and hypertensive states, by *Ray H. Rosenman*, $3,150.00

University of Washington School of Medicine, Seattle, for the study of factors influencing diastolic filling and systolic emptying of the ventricular chambers, by *Robert F. Rushmer*, $6,090.00

University of Wisconsin, Madison, for the study of the mechanism of pyruvate and α-ketoglutarate oxidation in heart muscle, by *D. Rao Sanadi*, $5,250.00

Irvington House, Irvington-on-Hudson, for the study of epidemiological studies of methods for prevention of rheumatic fever and rheumatic heart disease, by *Gene H. Stollerman*, $5,250.00

University of Colorado School of Medicine, Denver, for the study of the prevention and treatment of ventricular fibrillation during hypothermia, by *Henry Swan*, $5,250.00

Marine Biological Laboratory, Woods Hole, for the continuation of the research on the molecular basis of contraction, by *Albert Szent-Györgyi*, $10,000.00

Presbyterian Hospital, Chicago, for the study of an evaluation of the Macacus rhesus monkey as an experimental animal for the production of atherosclerosis including studies on cholesterol metabolism, by *C. Bruce Taylor*, $3,150.00

University of Louisville School of Medicine, Louisville, for the study of an investigation of the chemical and enzymatic composition of cardiac muscle granules, by *John Fuller Taylor*, $5,775.00

Southwestern Medical School of the University of Texas, Dallas, for further studies on the water and electrolyte content of arteries in relation to renal and steroid hypertension, to arterial actomyosin, and to drug induced arterial contraction and relaxation, by *Louis Tobian, Jr.*, $5,250.00

University of Minnesota, Minneapolis, for studies in intermediary metabolism, by *Richard W. von Korff*, $5,250.00

Yale University School of Medicine, New Haven, for the study of the modification of the lesions of experimental atherosclerosis, by *Levin Lyttleton Waters*, $5,250.00

Harvard Medical School, Boston, for an investigation of intravascular coagulation induced by stasis and the clot accelerating activity of serum (SPCA) under controlled conditions; an analysis of the factors influencing this mechanism, by *Stanford Wessler*, $4,200.00

Tulane University School of Medicine, New Orleans, for the study of effluographic determination of ion fluxes in heart muscle in relation to systole and the ECG, by *Walter S. Wilde*, $4,830.00

New York Hospital-Cornell University Medical Center, New York, for the study of electrostatic forces in blood coagulation and the mode of action of ionic anticoagulants, by *Irving S. Wright*, $6,300.00

APPLICATIONS FOR NEXT YEAR'S RESEARCH AWARDS

Applications for research awards to be made during the coming year by the American Heart Association and its affiliates throughout the country are now being accepted.

Applications for Research Fellowships and Established Investigatorships may be filed up to September 15, 1954. Applications for Research Grants-in-Aid will be accepted up to December 1, 1954. Information and forms may be obtained from the Medical Director, American Heart Association, 44 East 23rd Street, New York 10, N. Y.

The research awards will be available for studies to be conducted during the year beginning July 1, 1955. Funds to support the research program will be provided by the 1954 Heart Fund campaign conducted by the American Heart Association and its affiliated associations and chapters.

Established Investigatorships, awarded for one to five-year periods subject to annual review, range from $6,000 to $9,000. They are available to scientists of proven ability who are engaged in a research career. Research Fellowships, awarded for one or two-year periods, range from $3,500 to $5,500 and enable younger scientists to train for research careers under experienced supervision. Grants-in-Aid are awarded in varying amounts, usually

not exceeding $10,000, for periods of one to three years, to experienced scientists working in non-profit institutions on specified programs of research.

SECOND WORLD CONGRESS OF CARDIOLOGY AND 27TH SCIENTIFIC SESSIONS OF AMERICAN HEART ASSOCIATION

Registrations for the Second World Congress of Cardiology and the 27th Scientific Sessions of the American Heart Association have been received from physicians and research scientists in over 40 countries. The Congress will convene in Washington, D. C., September 12 through 17. *All those who are planning to participate are urged to submit their applications at the earliest possible date. Any physician who is interested may attend the Congress by filling out and sending in the application blank and paying the required registration fee.* Detailed information concerning the Congress and application blanks are available from the Secretary-General, L. W. Gorham, M.D., Second World Congress of Cardiology, c/o American Heart Association at 44 East 23rd Street, New York 10.

Schedule

A tentative schedule of the Congress follows:

Saturday, Sept. 11, 5:00 to 10:00 p.m.: Registration, Mayflower Hotel

Sunday, Sept. 12:

9:00 a.m. to 10:00 p.m.: Registration, Mayflower Hotel

10:30 a.m.: Opening ceremonies at Constitution Hall

9:00 p.m.: Reception, Pan American Building

Monday, Sept 13 through Friday, Sept. 17: Scientific Sessions at National Guard Armory. (See program below.)

Monday, Sept. 13, 8:30 to 10:30 p.m.: Visit to National Gallery of Art.

Tuesday, Sept. 14, 8:00 p.m.: Formal banquet, to be held simultaneously at Mayflower and Statler Hotels.

Wednesday, Sept. 15, 2:30 to 5:30 p.m.: Medical sightseeing tours.

Thursday, Sept. 16, 8:30 p.m.: Special entertainment (to be announced).

Friday, Sept. 17, 2:30 to 5:30 p.m.: Medical sightseeing tours.

Scientific Program

The scientific program of the Congress will be held at the National Guard Armory from Monday, September 13 through Friday, September 17. Morning sessions are scheduled daily from 9:00 a.m. to 12:30 p.m. Afternoon sessions will be held from 2:00 to 5:30 p.m. every day except Wednesday, Sept. 15 and Friday, Sept. 17 when medical tours are scheduled. Panels, symposia and special lectures will be held in the Main Auditorium. Simultaneous scientific sessions will be conducted in smaller rooms. The overall scientific program of the Congress is as follows:

Monday, Sept. 13

Main Auditorium—*9:00–10:30 a.m.:* International Cardiovascular Epidemiology; Introduction by Paul D. White, Boston. Atherosclerosis; Chairman, Ancel Keys, Minneapolis. *11:00 a.m.–12:30 p.m.:* Other Cardiovascular Relationships; Chairman, Paul D. White, Boston.

Simultaneous scientific sessions: Room 1, Electrocardiography (I). Room 2, Drugs and Therapy (I). Room 3, Physiology (I). Room 4, Occupational Cardiology and Rehabilitation.

Main Auditorium—*2:00–3:30 p.m.:* Diagnostic Methods in Congenital Heart Disease; Chairman, Andre Cournand, New York. *4:00–5:30 p.m.:* Congenital Heart Disease; Co-Chairmen, Helen B. Taussig, Baltimore; H. A. Snellen, Leiden, Netherlands.

Simultaneous scientific sessions: Room 1, Coronary Artery Disease. Room 2, Drugs and Therapy (II). Room 3, Physiology (II). Room 4, Mitral Stenosis.

Tuesday, Sept. 14

Main Auditorium—*9:00–11:00 a.m.:* Rheumatic Fever; Chairman, J. G. Fred Hiss, Syracuse, N. Y. Experimental Studies on Fibrinoids; Lewis Thomas, Minneapolis. Diagnosis and Management of Rheumatic Fever and Rheumatic Heart Disease, a panel presented by the Council on Rheumatic Fever and Congenital Heart Disease of the A. H. A.; Co-Chairmen, T. Duckett Jones, New York, Eric Bywaters, Berkshire, England. *11:30–12:30 p.m.:* George Brown Memorial Lecture, Alan Burton, London, Ontario, Canada.

Simultaneous scientific sessions: Room 1, Pulmonary Heart Disease. Room 2, Arteriosclerosis and Cerebrovascular Disease. Room 3, Electrocardiography (II). Room 4, Cardiovascular Surgery (I).

Main Auditorium—*2:00–3:30 p.m.:* Program presented by Section on Circulation of the A. H. A., Co-Chairmen, George E. Burch, New Orleans, Grace M. Roth, Rochester. *3:30–3:45 p.m.:* Paul White Prize Lecture of the Argentine Society of Cardiology; Methods for the Experimental Production of Generalized Atherosclerosis in the Rat. M. Rene Malinow, D. Hojman, A. A. Pellegrino, Buenos Aires. *4:00–5:30 p.m.:* Treatment of Hypertension; Co-chairmen, Eduardo Braun-Menendez, Buenos Aires; Irvine H. Page, Cleveland.

Simultaneous scientific sessions: Room 1, Rheumatic Fever and Rheumatic Heart Disease (I). Room 2, Ballistocardiography. Room 3, Electrocardiography (III). Room 4, Cardiovascular Surgery (II).

Wednesday, Sept. 15

Main Auditorium—*9:00–10:30 a.m.:* Blood Volume; Chairman, Gustav Nylin, Stockholm. *11:00–12:30 p.m.:* The Physiology of the Contractile Protein in Heart Muscle; Chairman, Maurice B. Visscher, Minneapolis.

Simultaneous scientific sessions: Room 1, Rheumatic Fever and Rheumatic Heart Disease (II). Room 2, Cardiopulmonary Dynamics. Room 3, Vectorcardiography. Room 4, Congenital Heart Disease (I).

Thursday, Sept. 16

Main Auditorium—*9:00–10:00 a.m.:* Surgery of Congenital Heart Disease; Co-chairmen: Alfred Blalock, Baltimore; Russell Brock, London. *10:30–12:30 p.m.:* Surgery of Non-congenital Heart Disease; Chairman, Robert Gross, Boston. *1130:1230 p.m.:* Vectorcardiography; Chairman, Pierre W. Duchosal, Geneva.

Simultaneous scientific sessions: Room 1, Peripheral Vascular Disease. Room 2, Heart Diseases of Uncommon Etiology (I). Room 3, Hypertension (I). Room 4, Diagnostic Methods.

Main Auditorium—*2:00–2:15 p.m.:* Memorial to Dr. Frank N. Wilson; Louis N. Katz, Chicago. *2:15–2:30 p.m.:* Memorial to Dr. Willem Einthoven; H. A. Snellen, Leiden, Netherlands. *2:30–4:00 p.m.:* Panel on Electrocardiography; Co-Chairmen, Louis N. Katz, Chicago, Charles E. Kossmann, New York, George E. Burch, New Orleans. *4:15–5:30 p.m.:* Ballistocardiography; Chairman, Isaac Starr, Philadelphia.

Simultaneous scientific sessions: Room 1, Heart Diseases of Uncommon Etiology (II). Room 2, Congenital Heart Disease (II). Room 3, Hypertension (II). Room 4, Phonocardiography and Auscultation.

Friday, Sept. 17

Main Auditorium—*9:00–10:30 a.m.:* Coronary Heart Disease; Chairman, Howard B. Sprague, Boston. *11:00–12:00 noon:* Charles Laubry Lecture, Sir John Parkinson, London. *12:00–12:30 p.m.:* Closing Remarks, Charles Laubry, Paris; Paul D. White, Boston.

Simultaneous scientific sessions: Room 1, Subacute Bacterial Endocarditis. Room 2, Diagnostic and Therapeutic Instruments. Room 3, Epidemiology. Room 4, X-Ray and Angiocardiography.

Medical Sightseeing Tours

A highlight of the Congress program will be a series of medical sightseeing tours to institutions of scientific interest. On Wednesday afternoon, September 15, participants may attend lectures, demonstrations and exhibits dealing with various aspects of cardiology which are planned at the George Washington University Hospital; Georgetown University Medical Center; Howard University Medical School; Children's Hospital; U. S. Veterans' Administration Hospital, Mt. Alto; Walter Reed Army Medical Center; Army Medical Service Graduate School; Research Laboratories of the Army Medical Service Graduate School; Armed Forces Institute of Pathology; and the National Naval Medical Center. The schedule will also include a Clinical Pathological Conference in the Main Auditorium of the National Guard Armory. A planned tour at the National Heart Institute of the U. S. Public Health Service will include the new research facility, the Clinical Center, and James Watt, M.D., Director of the National Heart Institute, and staff, will be available to discuss the Institute's program of research, grants, fellowships and traineeships.

A sightseeing program on Friday afternoon, September 17, will include conducted tours of the Armed Forces Institute of Pathology and its Medical Museum; Armed Forces Medical Library; and the National Heart Institute. The tour and discussion at the National Heart Institute will be repeated.

Post-Congressional Tours

A series of post-Congressional tours will include important University centers and cardiac clinics in the U. S. and Canada. A physician-member of the American Heart Association will accompany each tour. Because it is essential to make travel arrangements in advance, all those planning to participate are urged to write to the Secretary-General of the Congress for a descriptive booklet containing a form on which they may specify their choice of tours. *These forms should be filled out and returned at the earliest possible date.*

A schedule of the tours follows:

Tour A, Sept. 19–Sept. 29: Includes Washington, Baltimore, Philadelphia, New York, Boston.

Tour B, Sept. 28–Oct. 14: Includes Boston, Montreal, Toronto, Niagara Falls, Detroit, Ann Arbor, Chicago, Rochester, Minneapolis, Los Angeles, San Francisco.

Tour C, Sept. 28–Oct. 14: Includes Boston, Cleveland, Columbus, Cincinnati, St. Louis, Indianapolis, Chicago, Rochester, Minneapolis, Los Angeles, San Francisco, Seattle, New York.

Tour D, Sept. 28–Oct. 14: Includes Boston, Durham, Atlanta, Birmingham, New Orleans, Houston, Galveston, Los Angeles, San Francisco, Seattle, New York.

Membership

A registration fee of $25.00 has been established for the combined World Congress and Scientific Sessions. Although it has been customary in previous years to waive registration fees for professional members of the American Heart Association attending the Annual Scientific Sessions, the heavy expenses entailed by the enlarged and integrated sessions of the forthcoming Congress and the many events associated with an international meeting of this kind require that a fee be charged this year. The $25.00 fee entitles members to attend all scientific sessions, the opening reception, formal banquet and other social events planned for Congress delegates, the exhibits and special sightseeing tours to medical installations in Washington and its environs. Also included are the printed program, directory of registrants, Congressional badge and other items.

Associate membership (wives and family) has been arranged at a cost of $15.00. It will include all privileges mentioned above except the printed program. *A schedule of reduced fees has been provided for limited attendance by physicians and for attendance by such groups as medical students, interns and nurses.*

Exhibits

Scientific and industrial exhibits have been planned for the Congress, as well as a motion picture program of professional and scientific films on cardiovascular subjects. Those wishing to present scientific exhibits or films should communicate with Charles D. Marple, M.D., Medical Director of the Association. Industrial firms interested in presenting an exhibit should communicate with the Exhibit Manager, Steven K. Herlitz, 280 Madison Avenue, New York 16.

COURSE IN ELECTROCARDIOGRAPHIC INTERPRETATION

A course in electrocardiographic interpretation for graduate physicians will be given at the Michael Reese Hospital, Chicago, from August 2–14, 1954. The class will meet daily from 9 a.m. to 5 p.m. The course will be conducted by Louis N. Katz, M.D., Director of the Cardiovascular Department, Medical Research Institute, at the hospital, and his associates. Further information and a copy of the lecture schedule may be obtained from Mrs. Rivian H. Lewin, Administrative Secretary, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago 16, Ill.

MEETINGS

July 9–10: European Society of Cardiovascular Surgery; Edinburgh, Scotland; A. J. Slessor, Department of Surgery, University New Building, Edinburgh 8, Scotland.

July 12–22: International Gerontological Congress; London and Oxford, England; Professor R. E. Tunbridge, President, General Infirmary, Department of Medicine, The University, Leeds, England.

July 20–24: International Conference on Thrombosis and Embolism; Basle, Switzerland; W. Merz, M.D., Honorary Secretary, Chief Medical Officer, Gynecological Clinic, University of Basle.

August 9–13: National Medical Association; Washington, D. C.; John T. Givens, Secretary, 1108 Church Street, Norfolk 10, Va.

Sept. 6: American Society of Clinical Pathologists, Washington, D. C.; C. G. Culbertson, Secretary, 1040 W. Michigan Street, Indianapolis, Ind.

Sept. 6–10: International Congress of Clinical Pathology; Washington, D. C.; Dr. Robert A. Moore, Chairman, Committee on Arrangements, Washington University School of Medicine, St. Louis 10, Mo.

Sept. 6–11: Congress of Physical Medicine and Rehabilitation; Washington, D. C.; Francis Baker, Secretary, One Tilton Avenue, San Mateo, Calif.

Sept. 9–10: Vermont Heart Association and University of Vermont College of Medicine Seminar on Cardiac Arrhythmias; Burlington, Vt.; E. Lepeschkin, M.D., University of Vermont College of Medicine, Burlington, Vt.

Sept. 11: Vermont Heart Association and University of Vermont College of Medicine Symposium on the U wave of the Electrocardiogram; Burlington, Vt.; E. Lepeschkin, M.D., University of Vermont College of Medicine, Burlington, Vt.

Sept. 12–17: Second World Congress of Cardiology and the 27th Annual Scientific Sessions of the American Heart Association; Washington, D. C.; L. W. Gorham, M.D., Secretary-General, % the American Heart Association, 44 East 23rd Street, New York 10.

Sept. 26–Oct. 2: World Medical Association; Rome, Italy; Louis H. Bauer, Secretary, 345 East 46th Street, New York 17, N. Y.

Oct. 22–23: Annual Meeting and Scientific Program, Council for High Blood Pressure Research, American Heart Association, Cleveland; Irving S. Wright, M.D., Chairman, Program Committee, % American Heart Association, 44 East 23rd St., New York 10.

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